A 2-month-old boy is brought to the emergency department due to progressively worsening "floppiness" and poor feeding. The infant was born in Eastern Europe via an uncomplicated vaginal delivery to a 38-year-old woman and then immigrated to the United States with his family. The parents describe the infant as a "good baby" who rarely cries and sleeps through the night but has lately been difficult to rouse for breastfeeding. Stools have also decreased to every other day and are small and pellet-like. Physical examination shows a hypotonic infant with a large anterior fontanelle, large tongue, and a reducible umbilical hernia. He has low tone and is unable to hold his head erect on his own. No other abnormalities are seen. Which of the following is the most likely cause of this patient's condition?

- A. Botulism
- B. Down syndrome
- C. Galactosemia
- D. Hirschsprung disease
- E. Hypothyroidism
- F. Phenylketonuria

Submit

https://t.me/USMLEWorldStep1

A 2-month-old boy is brought to the emergency department due to progressively worsening "floppiness" and poor feeding. The infant was born in Eastern Europe via an uncomplicated vaginal delivery to a 38-year-old woman and then immigrated to the United States with his family. The parents describe the infant as a "good baby" who rarely cries and sleeps through the night but has lately been difficult to rouse for breastfeeding. Stools have also decreased to every other day and are small and pellet-like. Physical examination shows a hypotonic infant with a large anterior fontanelle, large tongue, and a reducible umbilical hernia. He has low tone and is unable to hold his head erect on his own. No other abnormalities are seen. Which of the following is the most likely cause of this patient's condition?

- ✗ A. Botulism (20%)
- B. Down syndrome (11%)
- C. Galactosemia (10%)
- D. Hirschsprung disease (5%)
- ✓ E. Hypothyroidism (41%)
- F. Phenylketonuria (9%)

Incorrect
Correct answer
E

41%
Answered correctly

02 mins, 02 secs
Time Spent

2023
Version

Explanation

Congenital hypothyroidism	
	• Usually asymptomatic at birth (rarely causes delayed meconium passage) • After maternal thyroxine wanes (weeks to months) ◦ Lethargy, poor feeding

https://t.me/USMLEWorldStep1

Congenital hypothyroidism	
Clinical manifestations	• Usually asymptomatic at birth (rarely causes delayed meconium passage) • After maternal thyroxine wanes (weeks to months) ◦ Lethargy, poor feeding ◦ Enlarged fontanelle ◦ Protruding tongue, puffy face, umbilical hernia ◦ Constipation ◦ Prolonged jaundice ◦ Dry skin
Diagnosis	• ↑ TSH & ↓ free thyroxine levels • Newborn screening
Treatment	• Levothyroxine*
Prognosis	• No deficits if treatment started in neonatal period • Untreated disease is associated with neurocognitive dysfunction (eg, ↓ intelligence quotient)
*Avoid coadministration with soy products, iron, or calcium.	

Congenital hypothyroidism is one of the most common causes of preventable intellectual disability. Most cases are due to thyroid dysgenesis (agenesis, hypoplasia, or ectopy), and iodine deficiency is a common cause in areas endemic for iodine deficiency (eg, Europe).

Neonates initially have no significant symptoms due to the presence of maternal thyroxine (T_4) from transplacental transfer. T_4 is responsible for the stimulation of protein synthesis as well as carbohydrate and lipid catabolism in many cells; as maternal T_4 wanes, metabolism is impaired and marked by a slowing of physical and mental activity (lethargy, poor feeding, constipation, hypotonia). Accumulation of matrix substances cutaneously and internally results in nonpitting edema (eg, "**puffy**" face), umbilical hernia, protruding tongue, and a large anterior fontanelle. In addition, T_4 is essential for normal brain development and myelination during early life, and infants are at risk of

https://t.me/USMLEWorldStep1

results in nonpitting edema (eg, "**puffy**" face), umbilical hernia, protruding tongue, and a large anterior fontanelle. In addition, T_4 is essential for normal brain development and myelination during early life, and infants are at risk of severe and **irreversible intellectual disability**.

Treatment with **levothyroxine** by age 2 weeks can normalize cognitive and physical development.

Therefore, universal newborn screening for congenital hypothyroidism is performed in the United States but not in all other countries.

(Choice A) Infants who are fed honey or exposed to spores from the soil are at risk for infantile botulism, which presents with constipation and flaccid paralysis. A large anterior fontanelle, umbilical hernia, and macroglossia are not seen.

(Choice B) Hypotonia and hypothyroidism are features of Down syndrome. However, the absence of other dysmorphic features (eg, upslanting palpebral fissures, bilateral epicanthal folds, single palmar crease) makes Down syndrome unlikely in this patient.

(Choice C) Galactosemia is caused by galactose-1-phosphate uridyltransferase deficiency. Patients with this condition present with jaundice, vomiting, hepatomegaly, and lethargy after ingesting galactose in breast milk or formula in the first few days of life. This patient was previously breastfeeding well and has no hepatomegaly.

(Choice D) Hirschsprung disease is caused by abnormal migration of neural crest cells into the rectosigmoid colon. The lack of ganglion cells in this colon segment impedes gastrointestinal motility, resulting in failed meconium passage and bilious emesis in a newborn.

(Choice F) Phenylketonuria is most commonly caused by phenylalanine hydroxylase deficiency, resulting in hyperphenylalaninemia. It presents with developmental delay, light pigmentation, and a musty body odor.

Educational objective:
Congenital hypothyroidism is usually asymptomatic at birth. After maternal T_4 wanes, infants develop constipation, lethargy, hypotonia, macroglossia, an umbilical hernia, and a large anterior fontanelle.

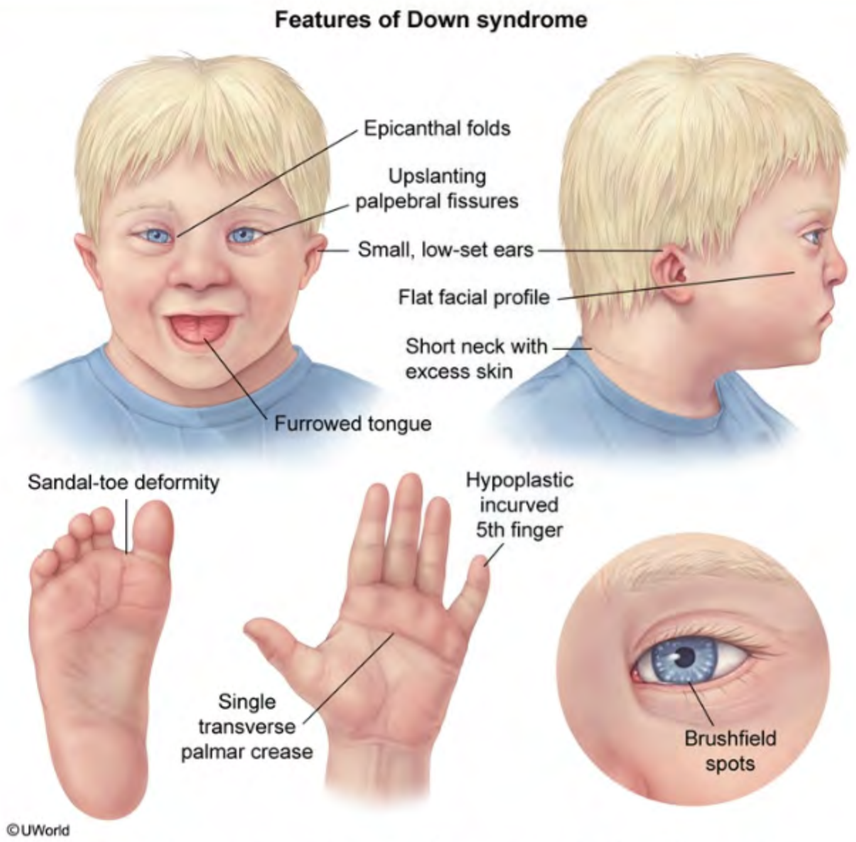
References

- Newborn screening for congenital hypothyroidism.
- Update of newborn screening and therapy for congenital hypothyroidism.

https://t.me/USMLEWorldStep1

are due to thyroid dysgenesis (agenesis, hypoplasia, or ectopy), and iodine deficiency is a common cause in areas
ender
Neona
transfe
many
(lethar
results
In add
severe
Treatn
Theref
all oth
(Choi
preser
not se
(Choi
dysmo
Down
(Choi
conditi
formul
(Choi
colon.
meconium passage and bilious emesis in a newborn.

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1
Show all

A 40-year-old man comes to the office due to erectile dysfunction and loss of libido. The patient's history is notable for Hodgkin lymphoma that was treated with chemotherapy. Physical examination is normal except for small testes. Laboratory evaluation shows consistently low total and free early morning testosterone levels and elevated serum LH. Transdermal testosterone therapy is prescribed. Which of the following should be periodically monitored during this patient's treatment?

- A. ECG
- B. Hematocrit
- C. Serum cortisol
- D. Serum creatinine
- E. Serum TSH and thyroxine

Submit

https://t.me/USMLEWorldStep1

A 40-year-old man comes to the office due to erectile dysfunction and loss of libido. The patient's history is notable for Hodgkin lymphoma that was treated with chemotherapy. Physical examination is normal except for small testes. Laboratory evaluation shows consistently low total and free early morning testosterone levels and elevated serum LH. Transdermal testosterone therapy is prescribed. Which of the following should be periodically monitored during this patient's treatment?

- A. ECG (5%)
- ✓ B. Hematocrit (48%)
- C. Serum cortisol (22%)
- D. Serum creatinine (6%)
- E. Serum TSH and thyroxine (16%)

Correct

48%
Answered correctly

04 secs
Time Spent

2023
Version

Explanation

Testosterone replacement therapy	
Indications	• Symptoms of hypogonadism • Consistently low serum testosterone
Contraindications	• Prostate cancer (elevated PSA) • Hematocrit >50% • Severe obstructive sleep apnea

https://t.me/USMLEWorldStep1
Show all

Explanation

Testosterone replacement therapy	
Indications	• Symptoms of hypogonadism • Consistently low serum testosterone
Contraindications	• Prostate cancer (elevated PSA) • Hematocrit >50% • Severe obstructive sleep apnea
Adverse effects	• Erythrocytosis • Venous thromboembolism
PSA = prostate-specific antigen.	

This patient has **hypogonadism** presenting with erectile dysfunction and loss of libido associated with a low serum testosterone level. Other common manifestations of hypogonadism include fatigue, loss of muscle mass, and decreased bone density. Hypogonadism is a common complication of cytotoxic chemotherapy (eg, cyclophosphamide) in long-term cancer survivors. **Testosterone replacement therapy** (TRT) is indicated for men with symptoms of hypogonadism and persistently low serum testosterone levels.

However, testosterone has trophic effects on the prostate, mediated by conversion to dihydrotestosterone by 5-alpha reductase in local tissues. TRT is associated with increased prostate volume, a rise in serum **prostate-specific antigen** (PSA), and a possible increase in the risk for prostate cancer. PSA should be measured prior to initiation of therapy and periodically thereafter.

In addition, TRT can induce **erythrocytosis**, possibly due to suppression of hepcidin and increased intestinal iron absorption. This can lead to increased blood viscosity and an elevated risk for thromboembolism. Therefore, TRT should not be initiated in patients with a baseline hematocrit >50%, and **hematocrit** should be followed regularly

https://t.me/USMLEWorldStep1
Show all

Contraindications	• Prostate cancer (elevated PSA) • Hematocrit >50% • Severe obstructive sleep apnea
Adverse effects	• Erythrocytosis • Venous thromboembolism
PSA = prostate-specific antigen.	

This patient has **hypogonadism** presenting with erectile dysfunction and loss of libido associated with a low serum testosterone level. Other common manifestations of hypogonadism include fatigue, loss of muscle mass, and decreased bone density. Hypogonadism is a common complication of cytotoxic chemotherapy (eg, cyclophosphamide) in long-term cancer survivors. **Testosterone replacement therapy** (TRT) is indicated for men with symptoms of hypogonadism and persistently low serum testosterone levels.

However, testosterone has trophic effects on the prostate, mediated by conversion to dihydrotestosterone by 5-alpha reductase in local tissues. TRT is associated with increased prostate volume, a rise in serum **prostate-specific antigen** (PSA), and a possible increase in the risk for prostate cancer. PSA should be measured prior to initiation of therapy and periodically thereafter.

In addition, TRT can induce **erythrocytosis**, possibly due to suppression of hepcidin and increased intestinal iron absorption. This can lead to increased blood viscosity and an elevated risk for thromboembolism. Therefore, TRT should not be initiated in patients with a baseline hematocrit >50%, and **hematocrit** should be followed regularly during treatment.

(Choice A) Some experts believe there is an increased risk of cardiovascular events associated with TRT and patients should be advised of this possibility. However, testing (eg, ECG) in asymptomatic patients is not necessary.

(Choices C and E) Patients with central/secondary hypogonadism (ie, low testosterone with low or inappropriately normal LH) should be tested for deficiencies in other hypothalamic-pituitary systems (eg, TSH + serum thyroxine,

https://t.me/USMLEWorldStep1
Show all

alpha reductase in local tissues. TRT is associated with increased prostate volume, a rise in serum **prostate-specific antigen** (PSA), and a possible increase in the risk for prostate cancer. PSA should be measured prior to initiation of therapy and periodically thereafter.

In addition, TRT can induce **erythrocytosis**, possibly due to suppression of hepcidin and increased intestinal iron absorption. This can lead to increased blood viscosity and an elevated risk for thromboembolism. Therefore, TRT should not be initiated in patients with a baseline hematocrit >50%, and **hematocrit** should be followed regularly during treatment.

(Choice A) Some experts believe there is an increased risk of cardiovascular events associated with TRT and patients should be advised of this possibility. However, testing (eg, ECG) in asymptomatic patients is not necessary.

(Choices C and E) Patients with central/secondary hypogonadism (ie, low testosterone with low or inappropriately normal LH) should be tested for deficiencies in other hypothalamic-pituitary systems (eg, TSH + serum thyroxine, morning cortisol). However, this patient has an elevated LH level consistent with primary hypogonadism, making these additional tests unnecessary.

(Choice D) Because renal toxicity is not a major concern with TRT, renal function does not need to be monitored.

Educational objective:
Testosterone replacement therapy is indicated for men with symptomatic hypogonadism. It is associated with an increase in serum prostate-specific antigen and may raise the risk of prostate cancer. In addition, testosterone therapy can cause erythrocytosis (leading to thromboembolism), and hematocrit should be regularly monitored.

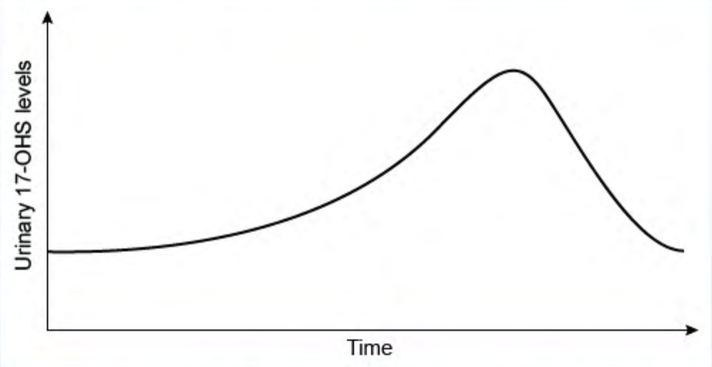
References

- Erythrocytosis following testosterone therapy.
- Hypogonadism in male cancer patients.

Pharmacology	Endocrine, Diabetes & Metabolism	Male sexual dysfunction
Subject	System	Topic

https://t.me/USMLEWorldStep1
Show all

A 60-year-old woman is being evaluated for chronic weakness and fatigue. She has no other medical problems and takes no medications. After performing initial laboratory studies, the physician decides to proceed with a metyrapone stimulation test. The changes in urinary 17-hydroxycorticosteroid (17-OHS) excretion following metyrapone administration are shown in the graph below.



Which of the following mechanisms is most likely responsible for the findings seen in the graph?

- A. ACTH surge
- B. Aldosterone overproduction
- C. Cortisol overproduction
- D. Renin surge
- E. Vasopressin overproduction

Submit

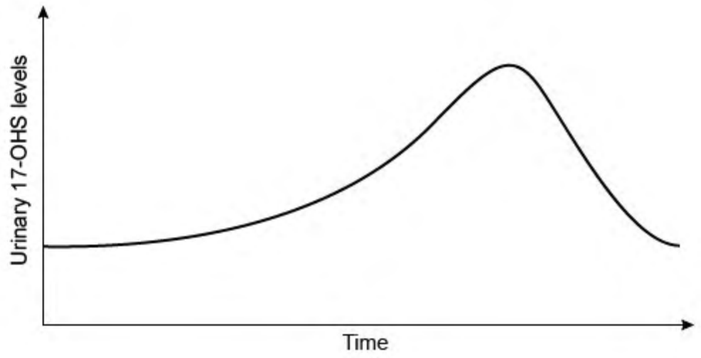
https://t.me/USMLEWorldStep1
Show all

A 60-year-old woman is being evaluated for chronic weakness and fatigue. She has no other medical problems
and ta
metyra
metyra

Which

Sub

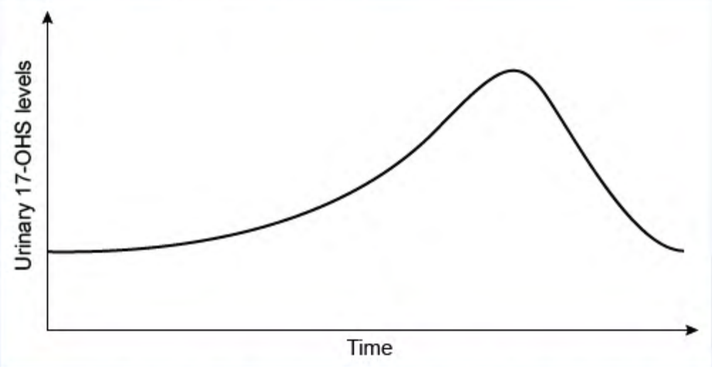
Exhibit Display



Zoom In Zoom Out Reset New | Existing My Notebook

https://t.me/USMLEWorldStep1
Show all

A 60-year-old woman is being evaluated for chronic weakness and fatigue. She has no other medical problems and takes no medications. After performing initial laboratory studies, the physician decides to proceed with a metyrapone stimulation test. The changes in urinary 17-hydroxycorticosteroid (17-OHS) excretion following metyrapone administration are shown in the graph below.



Which of the following mechanisms is most likely responsible for the findings seen in the graph?

- ✓ A. ACTH surge (63%)
- B. Aldosterone overproduction (8%)
- C. Cortisol overproduction (23%)
- D. Renin surge (2%)
- E. Vasopressin overproduction (1%)

Correct

63%
Answered correctly

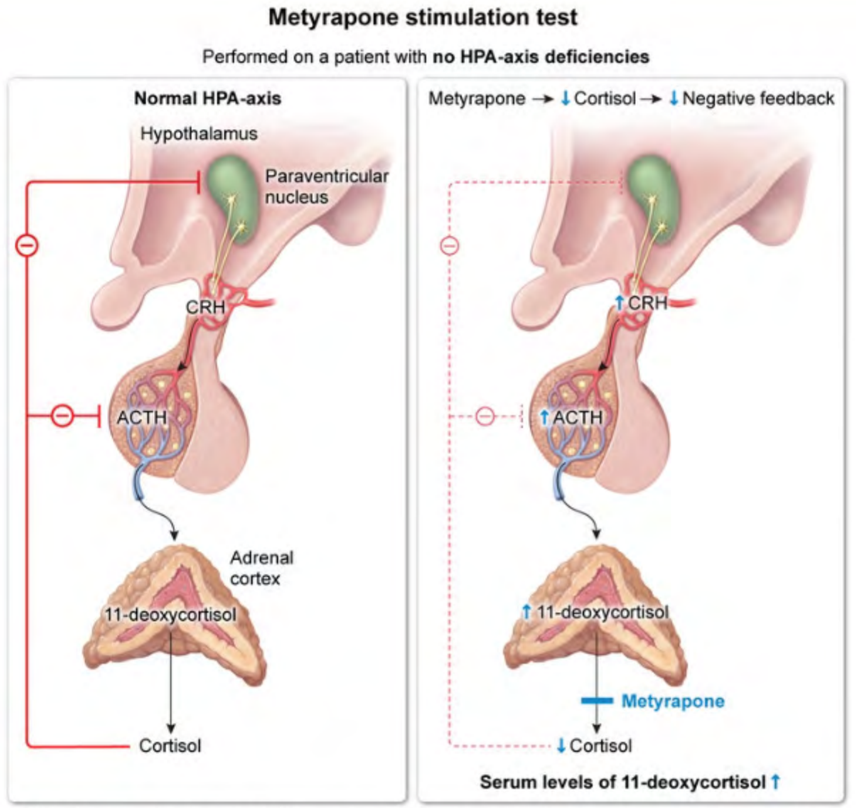
01 min, 26 secs
Time Spent

2023
Version

https://t.me/USMLEWorldStep1
Show all

Explanation

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Like most hormones, secretion of cortisol is regulated via a negative feedback loop. Corticotropin-releasing

https://t.me/USMLEWorldStep1
Show all



ACTH = adrenocorticotropic hormone; **CRH** = corticotropin releasing hormone; **HPA** = hypothalamic-pituitary-adrenal. ©UWorld

Like most hormones, secretion of cortisol is regulated via a negative feedback loop. Corticotropin-releasing hormone (CRH) is secreted by the hypothalamus in response to stress and circadian signals received from other parts of the central nervous system. CRH stimulates ACTH release by the pituitary, which in turn increases cortisol secretion by the adrenal cortex. High cortisol levels suppress secretion of ACTH and CRH, and low cortisol levels cause an increase in ACTH and CRH secretion.

Although not commonly used, the **metyrapone stimulation test** is a sensitive indicator of hypothalamic-pituitary-adrenal (HPA) axis integrity. Metyrapone blocks cortisol synthesis by inhibiting **11-β-hydroxylase**, which converts **11-deoxycortisol to cortisol** in the zona fasciculata. Because 11-deoxycortisol lacks glucocorticoid activity, it does not inhibit pituitary ACTH secretion. As a result, the reduction in cortisol levels following metyrapone administration cause an increase in pituitary ACTH secretion. This leads to increased production of 11-deoxycortisol, which is further metabolized by the liver to **17-hydroxycorticosteroids** that accumulate in the urine.

Serum 11-deoxycortisol and urinary 17-hydroxycorticosteroid levels will normally rise in response to metyrapone, indicating an intact HPA axis. Failure of these steroid levels to increase implies primary or secondary adrenal insufficiency, which can be distinguished based on plasma ACTH levels.

(Choices B and D) The renin-angiotensin-aldosterone system regulates aldosterone synthesis by the zona glomerulosa. Because metyrapone inhibits 11-β-hydroxylase, aldosterone synthesis will decrease. However, accumulation of the aldosterone precursor 11-deoxycorticosterone (a weak mineralocorticoid) prevents the development of mineralocorticoid deficiency, so renin levels will not change significantly.

(Choice C) The inhibition of 11-β-hydroxylase by metyrapone would lead to a decrease in cortisol, not an increase.

(Choice E) Vasopressin is a hormone secreted by the posterior pituitary that is responsible for regulating water balance. Additionally, vasopressin acts as a potentiator for CRH, enhancing the release of ACTH. However, there is no clear feedback loop between cortisol and vasopressin; therefore, metyrapone administration is unlikely to

https://t.me/USMLEWorldStep1
Show all

Although not commonly used, the **metyrapone stimulation test** is a sensitive indicator of hypothalamic-pituitary-adrenal (HPA) axis integrity. Metyrapone blocks cortisol synthesis by inhibiting **11-β-hydroxylase**, which converts **11-deoxycortisol to cortisol** in the zona fasciculata. Because 11-deoxycortisol lacks glucocorticoid activity, it does not inhibit pituitary ACTH secretion. As a result, the reduction in cortisol levels following metyrapone administration cause an increase in pituitary ACTH secretion. This leads to increased production of 11-deoxycortisol, which is further metabolized by the liver to **17-hydroxycorticosteroids** that accumulate in the urine.

Serum 11-deoxycortisol and urinary 17-hydroxycorticosteroid levels will normally rise in response to metyrapone, indicating an intact HPA axis. Failure of these steroid levels to increase implies primary or secondary adrenal insufficiency, which can be distinguished based on plasma ACTH levels.

(Choices B and D) The renin-angiotensin-aldosterone system regulates aldosterone synthesis by the zona glomerulosa. Because metyrapone inhibits 11-β-hydroxylase, aldosterone synthesis will decrease. However, accumulation of the aldosterone precursor 11-deoxycorticosterone (a weak mineralocorticoid) prevents the development of mineralocorticoid deficiency, so renin levels will not change significantly.

(Choice C) The inhibition of 11-β-hydroxylase by metyrapone would lead to a decrease in cortisol, not an increase.

(Choice E) Vasopressin is a hormone secreted by the posterior pituitary that is responsible for regulating water balance. Additionally, vasopressin acts as a potentiator for CRH, enhancing the release of ACTH. However, there is no clear feedback loop between cortisol and vasopressin; therefore, metyrapone administration is unlikely to lead to vasopressin overproduction.

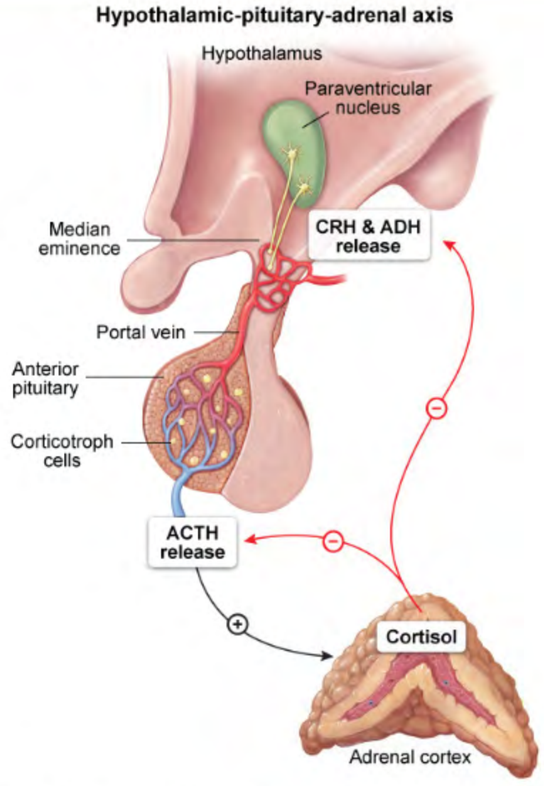
Educational objective:
Administration of metyrapone will cause a decrease in cortisol synthesis via inhibition of 11-β-hydroxylase. In patients with an intact hypothalamic-pituitary-adrenal axis, this will cause a reactive increase in ACTH, 11-deoxycortisol, and urinary 17-hydroxycorticosteroid levels.

Pathophysiology Endocrine, Diabetes & Metabolism Adrenal insufficiency

https://t.me/USMLEWorldStep1
Show all

Serum levels of 11-deoxycortisol ↑

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Like m
hormo
parts o
secret
cause

Althou
adrena
11-dec
does n
admin
deoxy

Serum
indicat
insuffi

(Choi
glome
accum
develo

(Choi
increa

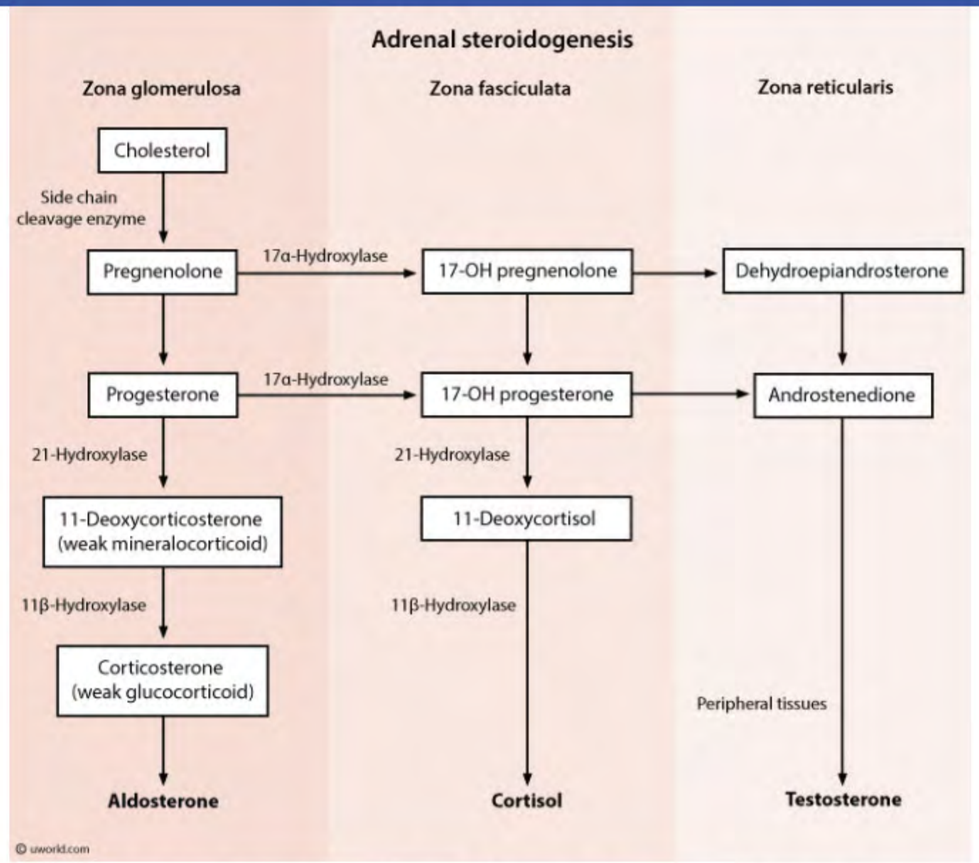
(Choi
balanc

is no clear feedback loop between cortisol and vasopressin; therefore, metyrapone administration is unlikely to

https://t.me/USMLEWorldStep1

Serum levels of 11-deoxycortisol ↑

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Like m
hormo
parts o
secret
cause

Althou
adrena
11-dec
does n
admin
deoxy

Serum
indicat
insuffi

(Choi
glome
accum
develo

(Choi
increa

(Choi
balanc

is no clear feedback loop between cortisol and vasopressin; therefore, metyrapone administration is unlikely to

https://t.me/USMLEWorldStep1

A 67-year-old man comes to the office due to increased fatigue and weight gain over the past 6 months. He has hypertension controlled with a calcium channel blocker. Two years ago, the patient's physical examination was unremarkable, and his blood tests, including a lipid panel, were normal. Blood pressure is 135/98 mm Hg, and pulse is 62/min. BMI is 28 kg/m^2. On physical examination, the thyroid appears to be mildly enlarged and is irregular and firm in consistency. Laboratory studies reveal elevated TSH, low free thyroxine (T4), high total and LDL cholesterol, and mildly elevated triglyceride levels. Which of the following is the most likely underlying mechanism for the elevated cholesterol in this patient?

- A. Activation of transcription factor peroxisome proliferator–activated receptor alpha
- B. Decreased LDL receptor gene expression
- C. Increased lipoprotein lipase gene expression
- D. Induction of HMG-CoA reductase
- E. Upregulation of LDL receptor degradation

Submit

https://t.me/USMLEWorldStep1

A 67-year-old man comes to the office due to increased fatigue and weight gain over the past 6 months. He has hypertension controlled with a calcium channel blocker. Two years ago, the patient's physical examination was unremarkable, and his blood tests, including a lipid panel, were normal. Blood pressure is 135/98 mm Hg, and pulse is 62/min. BMI is 28 kg/m^2. On physical examination, the thyroid appears to be mildly enlarged and is irregular and firm in consistency. Laboratory studies reveal elevated TSH, low free thyroxine (T4), high total and LDL cholesterol, and mildly elevated triglyceride levels. Which of the following is the most likely underlying mechanism for the elevated cholesterol in this patient?

- ✗ A. Activation of transcription factor peroxisome proliferator–activated receptor alpha (9%)
- ✓ B. Decreased LDL receptor gene expression (57%)
- C. Increased lipoprotein lipase gene expression (7%)
- D. Induction of HMG-CoA reductase (13%)
- E. Upregulation of LDL receptor degradation (11%)

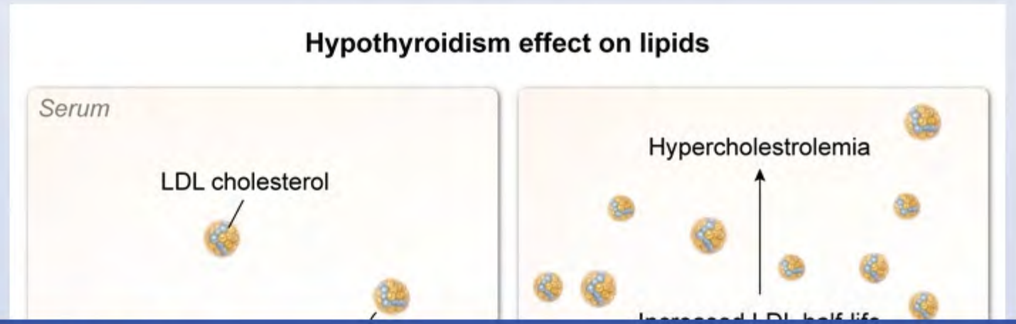
Incorrect
Correct answer
B

57%
Answered correctly

18 secs
Time Spent

2023
Version

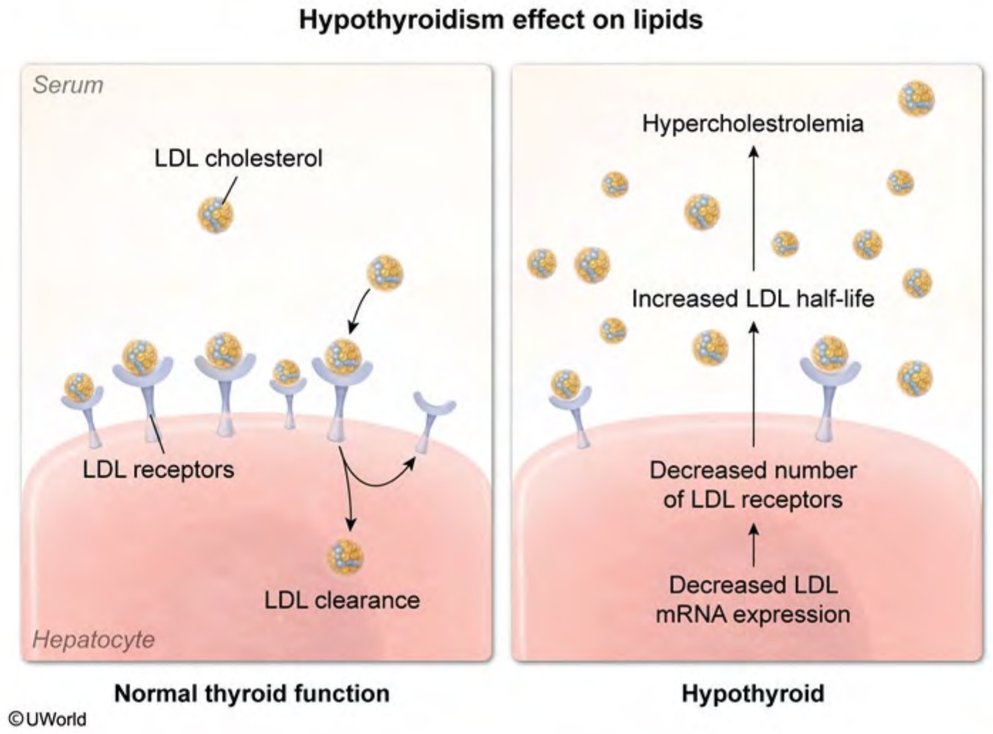
Explanation



https://t.me/USMLEWorldStep1

B. Decreased LDL receptor gene expression (57%)

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Normal thyroid function
Hypothyroid
©UWorld

https://t.me/USMLEWorldStep1



©UWorld

This patient has primary hypothyroidism presenting with fatigue, weight gain, and goiter, along with elevated TSH and low free thyroxine (T4) levels. **Hypothyroidism** can cause a number of adverse effects on serum lipids, including elevating total cholesterol, LDL cholesterol, and triglyceride levels.

Hypothyroidism causes **decreased LDL receptor expression**, leading to decreased clearance of LDL with resultant **increased blood LDL** levels. Hypothyroidism may also decrease LDL receptor activity and biliary excretion of cholesterol. Hypertriglyceridemia can occur in hypothyroidism due to decreased expression of lipoprotein lipase **(Choice C)**. Along with effects on blood pressure (eg, hypertension due to increased peripheral vascular resistance), the adverse effects of hypothyroidism on lipid levels can increase the risk of coronary atherosclerosis.

(Choice A) Peroxisome proliferator–activated receptor alpha (PPAR-α) stimulates fatty-acid uptake and beta oxidation; increased PPAR-α expression would cause a reduction in triglyceride levels. Decreased PPAR-α activity leads to hypertriglyceridemia and lipid accumulation within the liver (fatty liver disease) but is not associated with hypothyroidism.

(Choice D) Hypothyroidism is associated with decreased activity of HMG-CoA reductase and therefore decreased de novo synthesis of cholesterol; however, patients still develop hyperlipidemia due to reduced LDL clearance. Thyroid hormone (not hypothyroidism) induces expression of HMG-CoA reductase.

(Choice E) Similar to decreased LDL receptor expression, increased LDL receptor degradation leads to elevated blood LDL levels. Proprotein convertase subtilisin/kexin type 9 (PCSK9) increases the degradation of hepatic LDL receptors; alirocumab, a monoclonal antibody against PCSK9, blocks this effect, leading to a reduction in LDL levels. However, hypothyroidism is not associated with increased LDL receptor degradation.

Educational objective:
Hypothyroidism causes decreased expression of LDL receptors in the liver, leading to decreased clearance of LDL and increased blood LDL levels. It also causes hypertriglyceridemia due to decreased expression of lipoprotein lipase. The adverse effects of hypothyroidism on lipid levels can increase the risk of coronary atherosclerosis.

https://t.me/USMLEWorldStep1

A 33-year-old man comes to the office due to several months of episodic headaches accompanied by sweating and feelings of anxiety that spontaneously resolve after 15-30 minutes. The patient has no other medical conditions and takes no medications. His brother recently had surgery to treat hyperparathyroidism. Blood pressure is 180/110 mm Hg and pulse is 102/min. Laboratory results show normal serum electrolytes and renal function. CT scan of the abdomen reveals a mass in the right adrenal gland. Which of the following cells have the same embryologic origin as the tissue responsible for this patient's current condition?

- A. Capillary endothelial cells
- B. Cardiac myocytes
- C. Interstitial fibroblasts
- D. Melanin-producing cells
- E. Thyroid follicular cells

Submit

https://t.me/USMLEWorldStep1

A 33-year-old man comes to the office due to several months of episodic headaches accompanied by sweating and feelings of anxiety that spontaneously resolve after 15-30 minutes. The patient has no other medical conditions and takes no medications. His brother recently had surgery to treat hyperparathyroidism. Blood pressure is 180/110 mm Hg and pulse is 102/min. Laboratory results show normal serum electrolytes and renal function. CT scan of the abdomen reveals a mass in the right adrenal gland. Which of the following cells have the same embryologic origin as the tissue responsible for this patient's current condition?

- ✗ A. Capillary endothelial cells
- B. Cardiac myocytes
- C. Interstitial fibroblasts
- ✓ D. Melanin-producing cells
- E. Thyroid follicular cells

Incorrect
Correct answer
D

Collecting Statistics

03 secs
Time Spent

2023
Version

Explanation

Embryologic derivatives		
	Surface ectoderm	• Anterior pituitary (Rathke pouch) • Lens & cornea • Inner ear sensory organs, olfactory epithelium • Nasal & oral epithelial linings, salivary glands • Epidermis, sweat & mammary glands
		• Brain & spinal cord

https://t.me/USMLEWorldStep1

Embryologic derivatives		
Ectoderm	Surface ectoderm	• Anterior pituitary (Rathke pouch) • Lens & cornea • Inner ear sensory organs, olfactory epithelium • Nasal & oral epithelial linings, salivary glands • Epidermis, sweat & mammary glands
	Neural tube	• Brain & spinal cord • Posterior pituitary, pineal gland • Retina
	Neural crest	• Neural ganglia, adrenal medulla • Schwann cells; pia & arachnoid mater • Aorticopulmonary septum & endocardial cushions • Branchial arches (bones & cartilage) • Skull bones • Melanocytes
Mesoderm		• Muscles (skeletal, cardiac & smooth) • Connective tissue, bone & cartilage • Serosal linings (eg, peritoneum) • Cardiovascular & lymphatic system • Spleen & hemopoietic cells • Kidney & ureters, internal genitalia • Adrenal cortex
Endoderm		• Gastrointestinal tract, liver, pancreas • Lungs • Thymus, parathyroids, thyroid follicular cells • Middle ear epithelium

https://t.me/USMLEWorldStep1

Embryologic derivatives		
Ectoderm	Surface ectoderm	• Anterior pituitary (Rathke pouch) • Lens & cornea • Inner ear sensory organs, olfactory epithelium • Nasal & oral epithelial linings, salivary glands • Epidermis, sweat & mammary glands
	Neural tube	• Brain & spinal cord • Posterior pituitary, pineal gland • Retina
	Neural crest	• Neural ganglia, adrenal medulla • Schwann cells; pia & arachnoid mater • Aorticopulmonary septum & endocardial cushions • Branchial arches (bones & cartilage) • Skull bones • Melanocytes
Mesoderm		• Muscles (skeletal, cardiac & smooth) • Connective tissue, bone & cartilage • Serosal linings (eg, peritoneum) • Cardiovascular & lymphatic system • Spleen & hemopoietic cells • Kidney & ureters, internal genitalia • Adrenal cortex
Endoderm		• Gastrointestinal tract, liver, pancreas • Lungs • Thymus, parathyroids, thyroid follicular cells • Middle ear epithelium

https://t.me/USMLEWorldStep1

Ectoderm	Surface ectoderm	• Lens & cornea • Inner ear sensory organs, olfactory epithelium • Nasal & oral epithelial linings, salivary glands • Epidermis, sweat & mammary glands
	Neural tube	• Brain & spinal cord • Posterior pituitary, pineal gland • Retina
	Neural crest	• Neural ganglia, adrenal medulla • Schwann cells; pia & arachnoid mater • Aorticopulmonary septum & endocardial cushions • Branchial arches (bones & cartilage) • Skull bones • Melanocytes
Mesoderm		• Muscles (skeletal, cardiac & smooth) • Connective tissue, bone & cartilage • Serosal linings (eg, peritoneum) • Cardiovascular & lymphatic system • Spleen & hemopoietic cells • Kidney & ureters, internal genitalia • Adrenal cortex
Endoderm		• Gastrointestinal tract, liver, pancreas • Lungs • Thymus, parathyroids, thyroid follicular cells • Middle ear epithelium • Bladder & urethra • Parafollicular (C) cells*

*Formerly thought to be of neural crest origin.

https://t.me/USMLEWorldStep1

*Formerly thought to be of neural crest origin.	

This patient with hypertension; episodic headache, anxiety, and diaphoresis; and an adrenal mass on CT scan has a **pheochromocytoma**, a catecholamine-secreting tumor arising from the chromaffin cells of the **adrenal medulla**. Pheochromocytoma can be sporadic or associated with several familial disorders, especially multiple endocrine neoplasia (MEN) type 2 (likely in this patient given his family history of hyperparathyroidism).

The **chromaffin cells** of the adrenal medulla are derived from neural crest cells, which are multipotent, migratory cells that originate in the **ectoderm** at the margin of the neural tube and give rise to a diverse cell lineage. In addition to the adrenal medulla, other important structures that arise from neural crest cells include **melanocytes** (melanin-producing cells) and **neural ganglia** (eg, sympathetic and parasympathetic ganglia). Some cardiac (eg, aorticopulmonary septum, endocardial cushions) and skeletal (eg, skull/facial bones) structures are also derived from neural crest cells.

(Choices A, B, and C) Capillary endothelial cells, cardiac myocytes, and interstitial fibroblasts are mesodermal derivatives. Unlike the adrenal cortex, which is also derived from mesoderm, the adrenal medulla is a neural crest derivative.

(Choice E) Thyroid follicular cells are an endodermal derivative arising from the pharyngeal epithelium at the base of the tongue; parafollicular C cells are also an endodermal derivative, although they were previously thought to originate from the neural crest.

Educational objective:
Pheochromocytoma is a malignancy arising from chromaffin cells of the adrenal medulla that typically presents with episodic headaches, diaphoresis, and hypertension. The adrenal medulla is derived from neural crest cells (multipotent, migratory cells that originate in ectoderm), which also give rise to melanocytes and neural ganglia.

References

- Familial pheochromocytomas and paragangliomas.

Embryology	Endocrine, Diabetes & Metabolism	Pheochromocytoma
Subject	System	Topic

https://t.me/USMLEWorldStep1

- Spleen & hemopoietic cells
- Kidney & ureters, internal

Exhibit Display

Classification of multiple endocrine neoplasia	
Type 1	• **Primary hyperparathyroidism** (parathyroid adenomas or hyperplasia) • Pituitary tumors (prolactin, visual defects) • Pancreatic tumors (especially gastrinomas)
Type 2A	• **Medullary thyroid cancer** (calcitonin) • Pheochromocytoma • Primary hyperparathyroidism (parathyroid hyperplasia)
Type 2B	• **Medullary thyroid cancer** (calcitonin) • Pheochromocytoma • Mucosal neuromas/marfanoid habitus

New | Existing | My Notebook

This p
a **phe**
medu
endoc

The **cl**
cells t
additic
(melar
aortico
from n

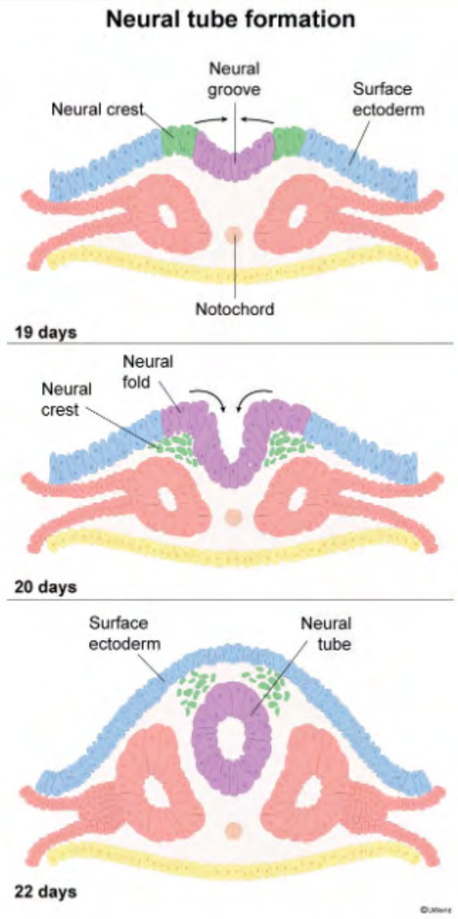
(Choi
deriva
derivative.

(Choice E) Thyroid follicular cells are an endodermal derivative arising from the pharyngeal epithelium at the base

https://t.me/USMLEWorldStep1

*Formerly thought to be of neural crest origin.

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

This p
a **phe**
medul
endoc

The **cl**
cells t
additic
(melar
aortico
from n

(Choi
deriva
deriva

(Choi
of the
origina

Educa
Pheoc
episoc
(multip

Refere
- Far

Embryology
Subject

Endocrine, Diabetes & Metabolism
System

Pheochromocytoma
Topic

https://t.me/USMLEWorldStep1

A 24-year-old postpartum woman comes to the office for follow-up of gestational diabetes. The patient was diagnosed with gestational diabetes mellitus during routine screening at 28 weeks gestation; she was treated with dietary modification and exercise and required insulin briefly. Since delivery 12 weeks ago, she has continued to follow dietary recommendations, and her blood glucose has been fairly well controlled without insulin. The patient has fasting blood glucose levels of 100-120 mg/dL. Medical history is otherwise unremarkable. Family history is significant for diabetes mellitus in her mother and gestational diabetes in her sister. Vital signs are within normal limits. BMI is 22 kg/m^2. Physical examination shows no abnormalities. Her gestational diabetes and fasting hyperglycemia are suspected to be genetically predisposed. This patient's condition is most likely caused by reduced activity of which of the following enzymes?

- A. Aldolase A
- B. Enolase
- C. Glucokinase
- D. Lactate dehydrogenase
- E. Phosphofructokinase
- F. Pyruvate carboxylase
- G. Pyruvate kinase

Submit

https://t.me/USMLEWorldStep1

A 24-year-old postpartum woman comes to the office for follow-up of gestational diabetes. The patient was diagnosed with gestational diabetes mellitus during routine screening at 28 weeks gestation; she was treated with dietary modification and exercise and required insulin briefly. Since delivery 12 weeks ago, she has continued to follow dietary recommendations, and her blood glucose has been fairly well controlled without insulin. The patient has fasting blood glucose levels of 100-120 mg/dL. Medical history is otherwise unremarkable. Family history is significant for diabetes mellitus in her mother and gestational diabetes in her sister. Vital signs are within normal limits. BMI is 22 kg/m^2. Physical examination shows no abnormalities. Her gestational diabetes and fasting hyperglycemia are suspected to be genetically predisposed. This patient's condition is most likely caused by reduced activity of which of the following enzymes?

- ✗ A. Aldolase A (3%)
- B. Enolase (1%)
- ✓ C. Glucokinase (57%)
- D. Lactate dehydrogenase (2%)
- E. Phosphofructokinase (22%)
- F. Pyruvate carboxylase (6%)
- G. Pyruvate kinase (5%)

Incorrect
Correct answer
C

57%
Answered correctly

04 secs
Time Spent

2023
Version

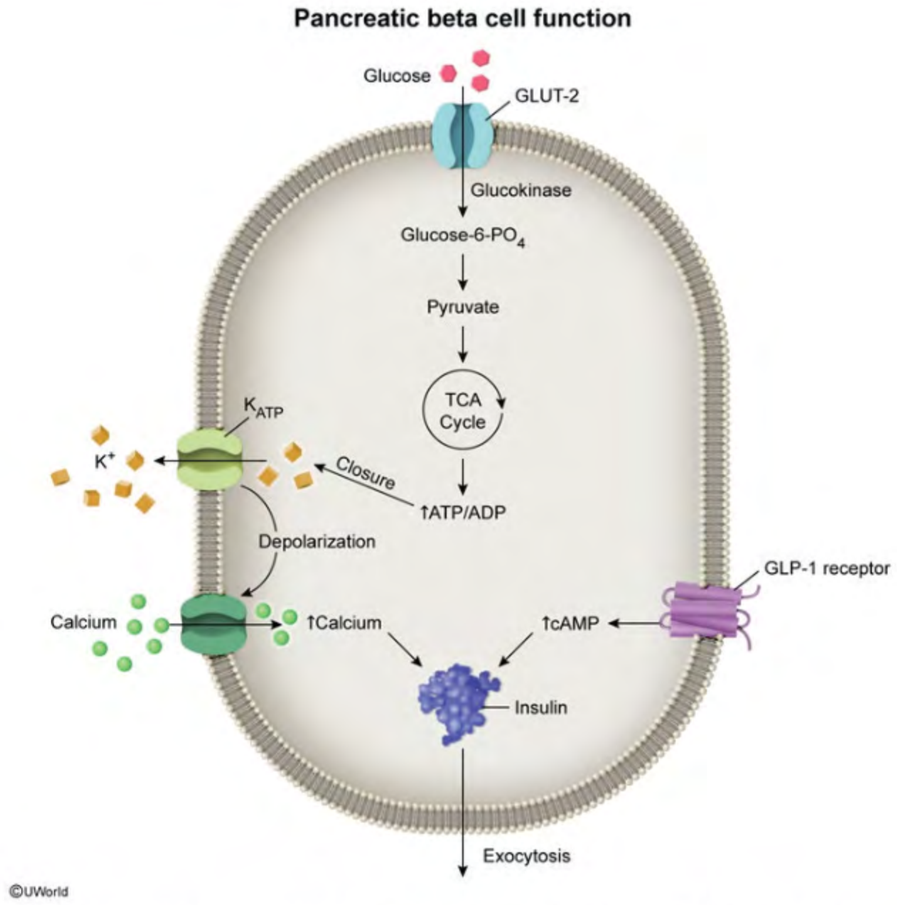
Explanation



https://t.me/USMLEWorldStep1

Explanation

Exhibit Display

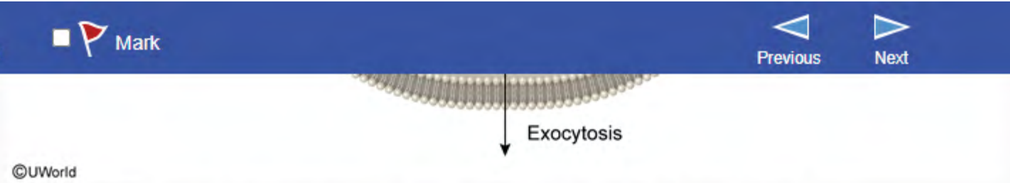


Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Glucos

1. Glucose enters the beta cell through glucose transporter type 2 (GLUT-2).

https://t.me/USMLEWorldStep1



Glucose-induced insulin release from pancreatic beta cells requires the following steps:

1. Glucose enters the beta cell through glucose transporter type 2 (GLUT-2).
2. Glucose is metabolized by glucokinase to glucose-6-phosphate.
3. Glucose-6-phosphate enters glycolysis to produce ATP.
4. Increased ATP levels causes closure of ATP-sensitive potassium (K_{ATP}) channels.
5. Depolarization of beta cells triggers opening of voltage-dependent calcium channels.
6. Influx of calcium causes insulin release.

Glucokinase has a lower glucose affinity than other hexokinases, which allows it to limit the rate of glucose entry into the glycolytic pathway based on blood glucose levels. It therefore functions as a **glucose sensor** for beta cells in controlling insulin release.

Heterozygous mutations of the glucokinase gene that decrease the activity or affinity of the enzyme cause a decrease in beta cell glucose metabolism, leading to reduced ATP formation and insulin secretion at any given glucose level. Glucokinase mutations are one cause of **maturity-onset diabetes of the young (MODY)**, an autosomal dominant disorder characterized by **mild hyperglycemia** that often worsens with pregnancy-induced insulin resistance. In contrast to those with more common type 2 diabetes mellitus, patients with MODY are typically younger and nonobese, and the condition is **nonprogressive**, even without treatment.

(Choices A, B, E, and G) Glycolytic enzyme deficiencies (eg, aldolase A, enolase, phosphofructokinase, pyruvate kinase) generally present with hemolytic anemia because red blood cells rely completely on anaerobic glycolysis for energy production.

(Choice D) Lactate dehydrogenase is present in most cells and catalyzes the conversion of pyruvate to lactate during anaerobic glycolysis. Deficiency can cause decreased exercise tolerance and muscle stiffness.

(Choice F) Pyruvate carboxylase, one of the gluconeogenesis pathway enzymes in the mitochondria, catalyzes the conversion of pyruvate to oxaloacetate. Deficiency of pyruvate carboxylase causes lactic acidosis and fasting hypoglycemia.

https://t.me/USMLEWorldStep1

3. Glucose-6-phosphate enters glycolysis to produce ATP.
4. Increased ATP levels causes closure of ATP-sensitive potassium (K_{ATP}) channels.
5. Depolarization of beta cells triggers opening of voltage-dependent calcium channels.
6. Influx of calcium causes insulin release.

Glucokinase has a lower glucose affinity than other hexokinases, which allows it to limit the rate of glucose entry into the glycolytic pathway based on blood glucose levels. It therefore functions as a **glucose sensor** for beta cells in controlling insulin release.

Heterozygous mutations of the glucokinase gene that decrease the activity or affinity of the enzyme cause a decrease in beta cell glucose metabolism, leading to reduced ATP formation and insulin secretion at any given glucose level. Glucokinase mutations are one cause of **maturity-onset diabetes of the young (MODY)**, an autosomal dominant disorder characterized by **mild hyperglycemia** that often worsens with pregnancy-induced insulin resistance. In contrast to those with more common type 2 diabetes mellitus, patients with MODY are typically younger and nonobese, and the condition is **nonprogressive**, even without treatment.

(Choices A, B, E, and G) Glycolytic enzyme deficiencies (eg, aldolase A, enolase, phosphofructokinase, pyruvate kinase) generally present with hemolytic anemia because red blood cells rely completely on anaerobic glycolysis for energy production.

(Choice D) Lactate dehydrogenase is present in most cells and catalyzes the conversion of pyruvate to lactate during anaerobic glycolysis. Deficiency can cause decreased exercise tolerance and muscle stiffness.

(Choice F) Pyruvate carboxylase, one of the gluconeogenesis pathway enzymes in the mitochondria, catalyzes the conversion of pyruvate to oxaloacetate. Deficiency of pyruvate carboxylase causes lactic acidosis and fasting hypoglycemia.

Educational objective:
Insulin release by pancreatic beta cells is stimulated by increased glucose metabolism and ATP production. Glucokinase functions as a glucose sensor in pancreatic beta cells by controlling the rate of glucose entry into the glycolytic pathway. Mutations in the glucokinase gene lead to a state in which higher glucose levels are required to stimulate insulin secretion and are a cause of maturity-onset diabetes of the young.

References

https://t.me/USMLEWorldStep1

A 58-year-old man comes to the office for evaluation of a thyroid nodule. The patient first noticed a painless neck lump 2 months ago, which has progressively enlarged. He has had no heat or cold intolerance, recent weight changes, or difficulty breathing or swallowing. Medical history is notable for well-controlled hypertension. The patient has no history of radiation exposure or family history of thyroid diseases. Physical examination shows a firm, nontender nodule in the right thyroid lobe. Serum TSH level is normal, and ultrasonography shows a 4-cm solid nodule in the right thyroid lobe. Fine-needle aspiration biopsy shows a large number of follicular cells dispersed in clusters and microfollicles. The patient undergoes right thyroid lobectomy. Which of the following histologic findings would confirm a diagnosis of follicular thyroid carcinoma in this patient?

- A. C-cell hyperplasia
- B. Cells with empty appearing nuclei
- C. Hürthle cells
- D. Lymphocytic germinal centers
- E. Multinucleated giant cells
- F. Tumor capsular invasion

Submit

https://t.me/USMLEWorldStep1

A 58-year-old man comes to the office for evaluation of a thyroid nodule. The patient first noticed a painless neck lump 2 months ago, which has progressively enlarged. He has had no heat or cold intolerance, recent weight changes, or difficulty breathing or swallowing. Medical history is notable for well-controlled hypertension. The patient has no history of radiation exposure or family history of thyroid diseases. Physical examination shows a firm, nontender nodule in the right thyroid lobe. Serum TSH level is normal, and ultrasonography shows a 4-cm solid nodule in the right thyroid lobe. Fine-needle aspiration biopsy shows a large number of follicular cells dispersed in clusters and microfollicles. The patient undergoes right thyroid lobectomy. Which of the following histologic findings would confirm a diagnosis of follicular thyroid carcinoma in this patient?

- ✗ A. C-cell hyperplasia (4%)
- B. Cells with empty appearing nuclei (7%)
- C. Hürthle cells (8%)
- D. Lymphocytic germinal centers (6%)
- E. Multinucleated giant cells (1%)
- ✓ F. Tumor capsular invasion (71%)

Incorrect
Correct answer
F

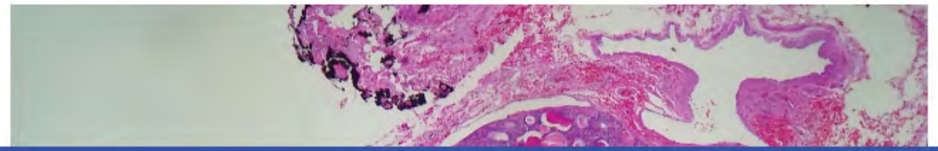
71%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

Follicular thyroid carcinoma

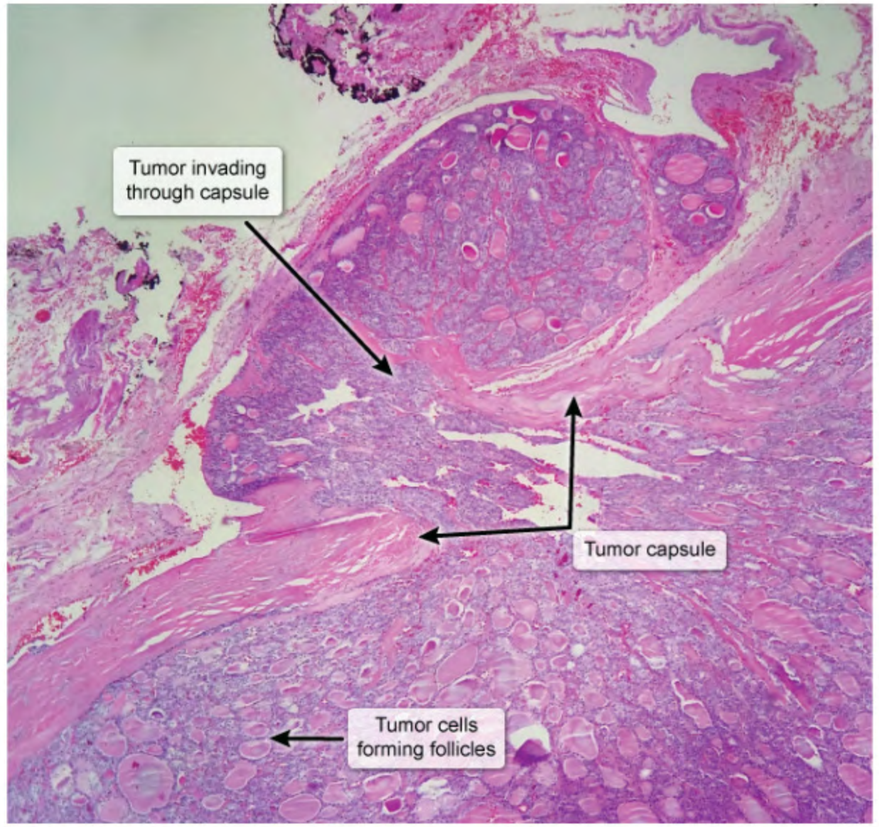


https://t.me/USMLEWorldStep1

A 58-year-old man comes to the office for evaluation of a thyroid nodule. The patient first noticed a painless neck lump 2
chang
patien
firm, n
solid n
disper
histolo

Exhibit Display

Follicular thyroid carcinoma



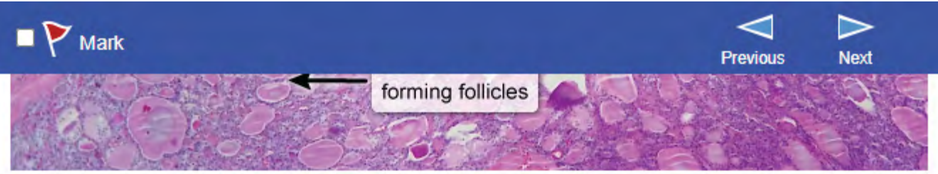
©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Inco
Corre
F

Expl

https://t.me/USMLEWorldStep1



©UWorld

This euthyroid patient has a slowly enlarging, firm, painless thyroid nodule and fine-needle aspiration (FNA) results indicative of a **follicular neoplasm** (eg, numerous follicular cells and microfollicles). Most follicular thyroid neoplasms are benign follicular adenomas, but 15%-30% can be malignant follicular carcinomas. Both types of follicular neoplasms have a similar appearance on ultrasound and FNA.

Differentiating between benign and malignant follicular lesions can only be accomplished by histologic examination of the entire tumor (eg, thyroidectomy).

- Follicular adenomas (the most common benign thyroid neoplasm) display numerous neoplastic follicular cells and microfollicles on histology but are completely encapsulated.
- In contrast, **follicular thyroid carcinomas** are characterized by **invasion of the tumor capsule** and/or surrounding blood vessels.

This propensity of follicular thyroid carcinomas to invade surrounding blood vessels accounts for their tendency to metastasize via **hematogenous spread** to distant tissues (eg, bone, lung).

(Choice A) Medullary thyroid carcinomas can develop sporadically or in patients with an inherited *RET* proto-oncogene mutation (eg, multiple endocrine neoplasia 2a or 2b). In patients with this germline mutation, C-cell hyperplasia is often found as a precursor to a malignant lesion. Malignant C cells secrete calcitonin, which can form amyloid deposits within the tumor.

(Choice B) Papillary thyroid carcinoma (the most common type of thyroid malignancy) has distinct cytologic and histologic features. These include laminar calcifications (psammoma bodies), large cells with pale, empty-appearing nuclei (Orphan Annie–eye or ground-glass nuclei) with nuclear inclusion bodies and nuclear grooves. Unlike FTC, papillary thyroid carcinoma can be diagnosed on FNA results.

(Choice C) Hürthle cells are large, polygonal cells with granular, eosinophilic cytoplasm due to large quantities of mitochondria. They are a nonspecific finding seen in a wide variety of neoplastic and nonneoplastic thyroid lesions. Therefore, they would not be of benefit in differentiating between benign and malignant follicular lesions.

https://t.me/USMLEWorldStep1

surrounding blood vessels.

This propensity of follicular thyroid carcinomas to invade surrounding blood vessels accounts for their tendency to metastasize via **hematogenous spread** to distant tissues (eg, bone, lung).

(Choice A) Medullary thyroid carcinomas can develop sporadically or in patients with an inherited *RET* proto-oncogene mutation (eg, multiple endocrine neoplasia 2a or 2b). In patients with this germline mutation, C-cell hyperplasia is often found as a precursor to a malignant lesion. Malignant C cells secrete calcitonin, which can form amyloid deposits within the tumor.

(Choice B) Papillary thyroid carcinoma (the most common type of thyroid malignancy) has distinct cytologic and histologic features. These include laminar calcifications (psammoma bodies), large cells with pale, empty-appearing nuclei (Orphan Annie–eye or ground-glass nuclei) with nuclear inclusion bodies and nuclear grooves. Unlike FTC, papillary thyroid carcinoma can be diagnosed on FNA results.

(Choice C) Hürthle cells are large, polygonal cells with granular, eosinophilic cytoplasm due to large quantities of mitochondria. They are a nonspecific finding seen in a wide variety of neoplastic and nonneoplastic thyroid lesions. Therefore, they would not be of benefit in differentiating between benign and malignant follicular lesions.

(Choice D) Chronic autoimmune (Hashimoto) thyroiditis typically presents with signs of primary hypothyroidism (eg, weight gain, cold intolerance, elevated TSH) due to autoimmune destruction of the thyroid gland. Histology shows inflammation and lymphocytic germinal centers in the thyroid gland.

(Choice E) Multinucleated giant cells are seen in many thyroid conditions, including thyroiditis, cystic degeneration, and papillary thyroid carcinoma. They are not typically seen in follicular lesions.

Educational objective:
Follicular neoplasms typically present as slowly enlarging, painless thyroid nodules. Differentiation between a follicular adenoma and follicular thyroid carcinoma is not possible using only fine-needle aspiration results. Histologic evidence of invasion of the tumor capsule and/or surrounding blood vessels is needed to diagnose follicular thyroid carcinoma.

Pathology	Endocrine, Diabetes & Metabolism	Thyroid cancer
Subject	System	Topic

https://t.me/USMLEWorldStep1

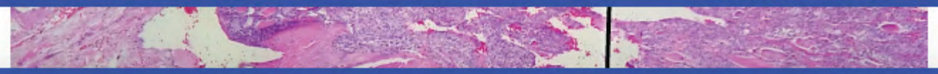
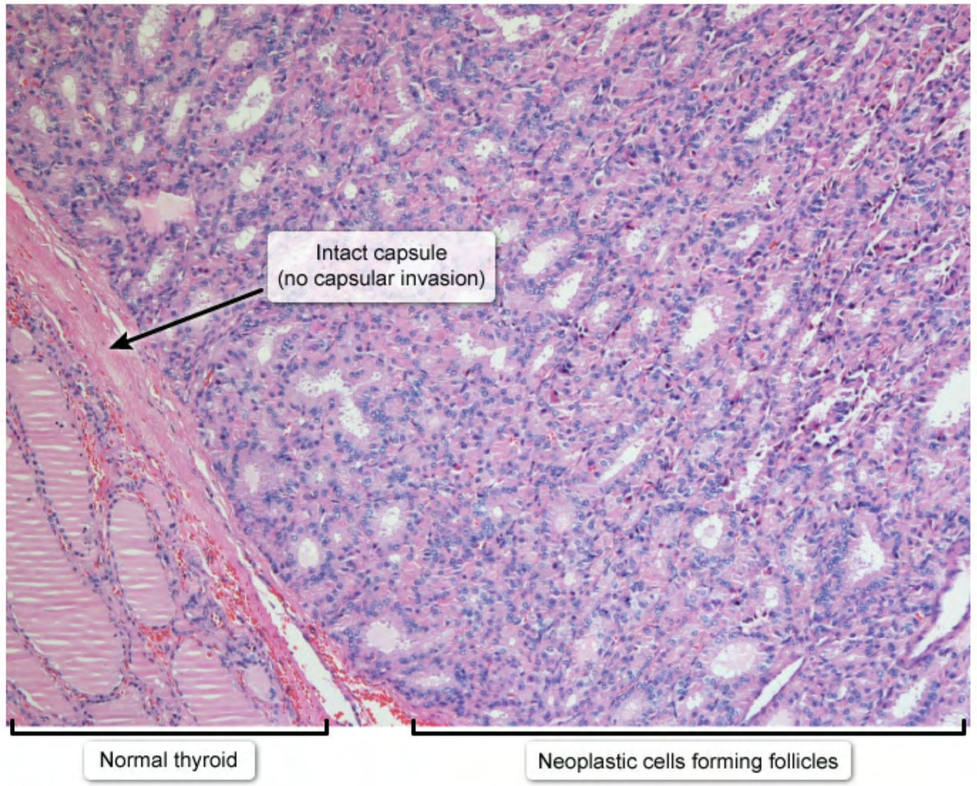


Exhibit Display

Follicular adenoma



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

This e
indicat
neopla
follicul

Differe
of the

- F
  a
- In
  st

This p
metas

(Choi
oncog
hyperp
form a

(Choice B) Papillary thyroid carcinoma (the most common type of thyroid malignancy) has distinct cytologic and

https://t.me/USMLEWorldStep1

This euthyroid patient has a slowly enlarging, firm, painless thyroid nodule and fine-needle aspiration (FNA) results indicative of a **follicular neoplasm** (eg, numerous follicular cells and microfollicles). Most follicular thyroid neopla
follicul

Differe
of the

- F
  a
- In
  su

This p
metas

(Choi
oncog
hyperp
form a

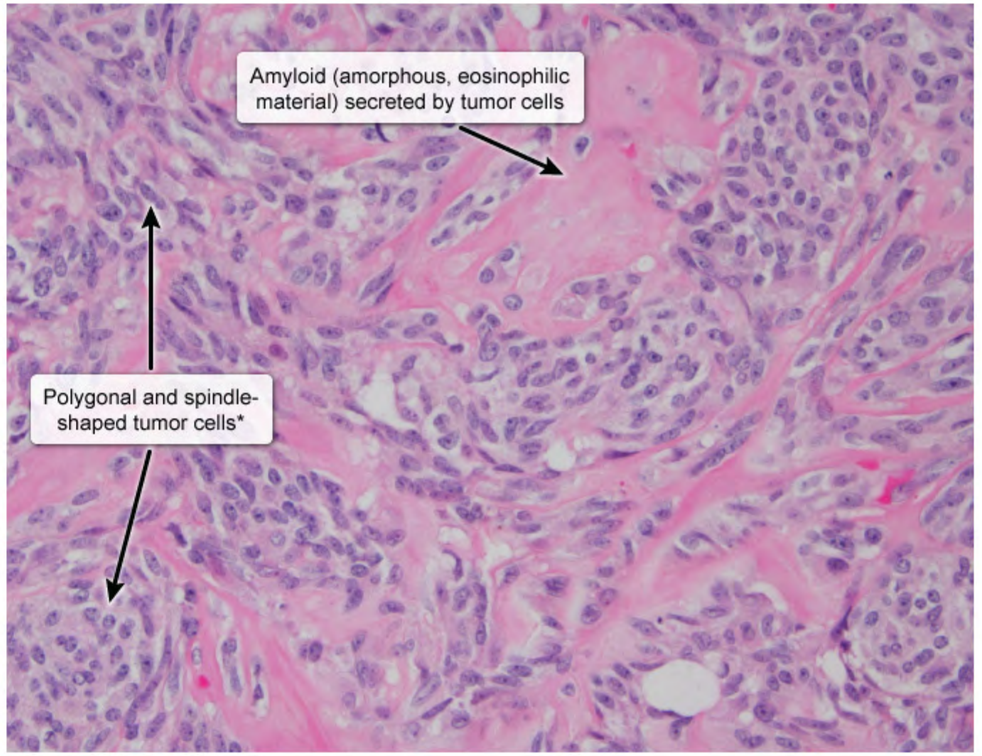
(Choi
histolo
appea
Unlike

(Choi
mitoch
lesions

(Choi
(eg, w
shows inflammation and lymphocytic germinal centers in the thyroid gland.

Exhibit Display

Medullary thyroid carcinoma



*Derived from C (parafollicular) cells.

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

This euthyroid patient has a slowly enlarging, firm, painless thyroid nodule and fine-needle aspiration (FNA) results indicative of a **follicular neoplasm** (eg, numerous follicular cells and microfollicles). Most follicular thyroid neopla
follicul

Differe
of the

- F
  a
- In
  s

This p
metas

(Choi
oncog
hyperp
form a

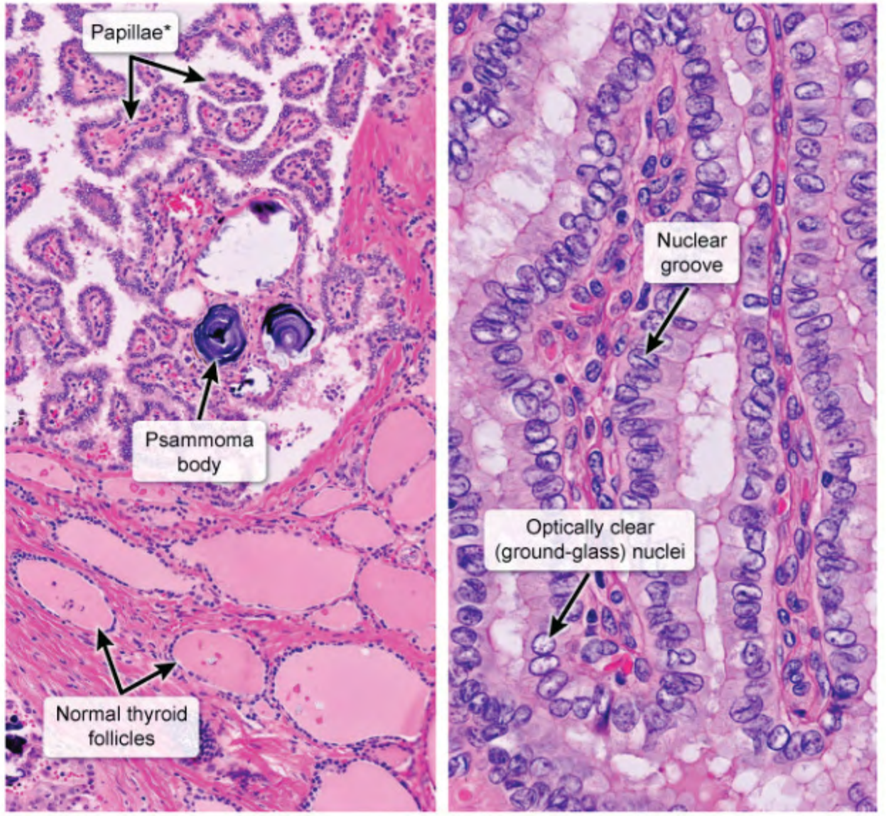
(Choi
histolo
appea
Unlike

(Choi
mitoch
lesions

(Choi
(eg, w
shows inflammation and lymphocytic germinal centers in the thyroid gland.

Exhibit Display

Papillary thyroid carcinoma



*Fibrovascular cores lined by epithelial cells

©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

follicular neoplasms have a similar appearance on ultrasound and FNA.

Differentiating between benign and malignant follicular lesions can only be accomplished by histologic examination of the

- F a
- In s

This p metas

(Choi oncog hyperp form a

(Choi histolo appea Unlike

(Choi mitoch lesions

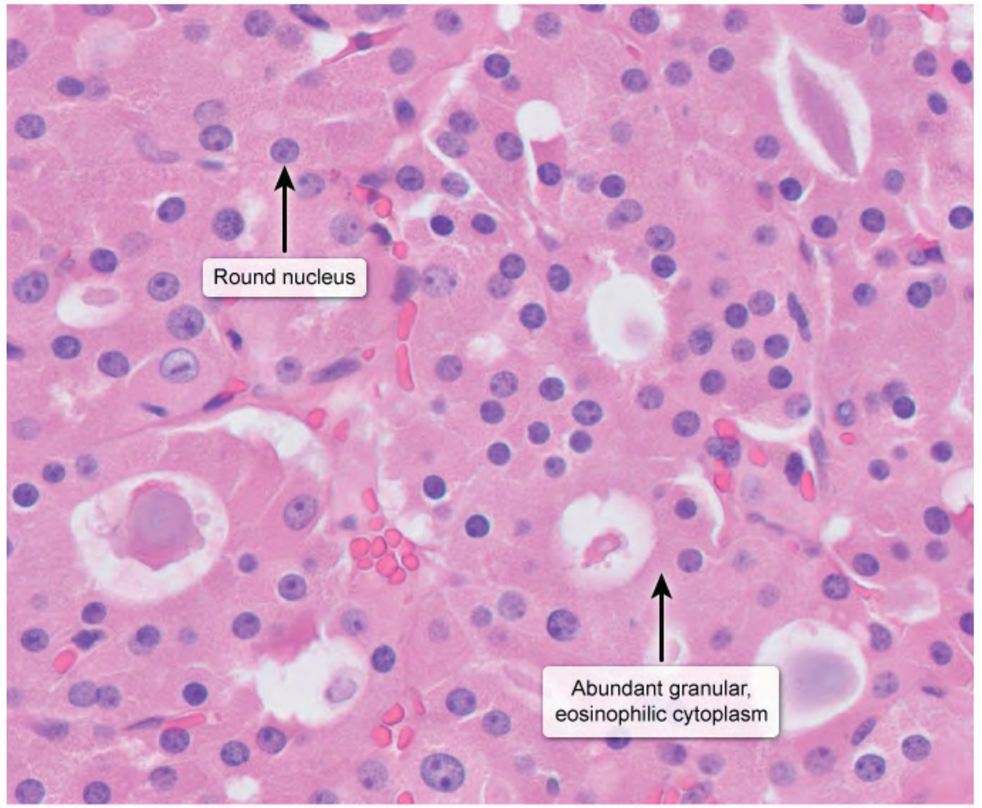
(Choi (eg, w shows

(Choi degen

Educational objective:

Exhibit Display

Hürthle cells



©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

- Follicular adenomas (the most common benign thyroid neoplasm) display numerous neoplastic follicular cells and microfollicles on histology but are completely encapsulated.
- In

This p
metas

(Choi
oncog
hyperp
form a

(Choi
histolo
appea
Unlike

(Choi
mitoch
lesions

(Choi
(eg, w
shows

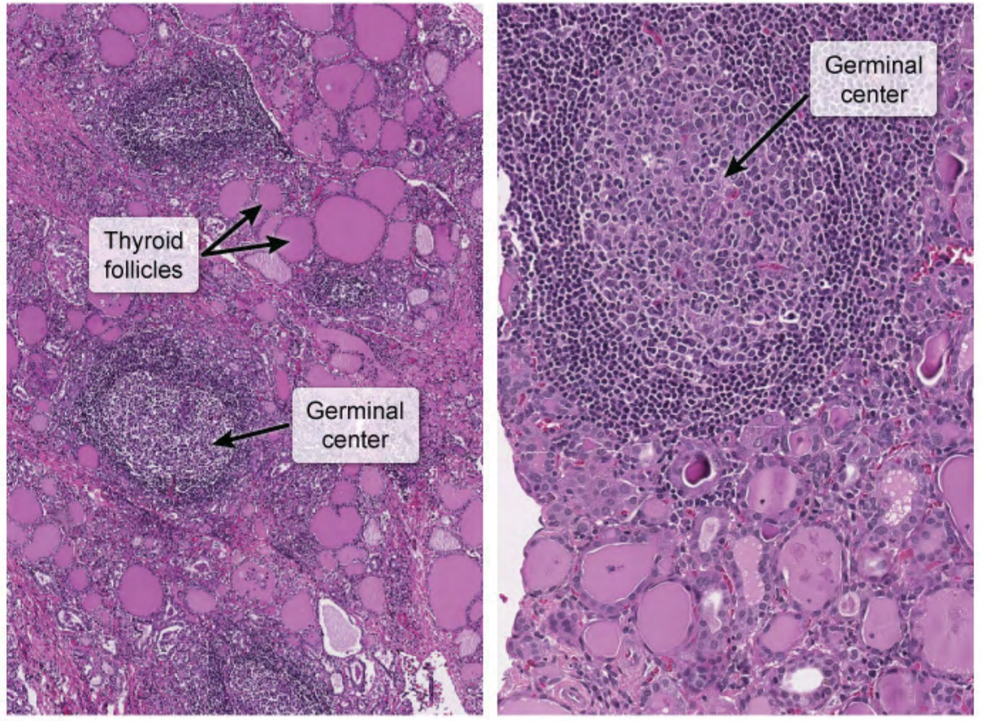
(Choi
degen

Educa
Follicu
follicul

Histologic evidence of invasion of the tumor capsule and/or surrounding blood vessels is needed to diagnose

Exhibit Display

Hashimoto thyroiditis



©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

A 55-year-old woman is diagnosed with breast cancer and undergoes breast-sparing mastectomy. The tumor margin did not show any invasion, and sentinel axillary lymph node biopsy was negative for nodal metastasis. The tumor was estrogen receptor and progesterone receptor positive but HER-2 negative. After discussion of management options, the patient is started on tamoxifen. While on this medication, she experiences hot flashes that come and go in waves and affect her sleep significantly. Which of the following conditions is the patient also likely to experience as a result of this therapy?

- A. Decrease in bone mass
- B. Decrease in HDL level
- C. Endometrial hyperplasia
- D. Fibroadenoma of the breast
- E. Increase in LDL level

Submit

https://t.me/USMLEWorldStep1

A 55-year-old woman is diagnosed with breast cancer and undergoes breast-sparing mastectomy. The tumor margin did not show any invasion, and sentinel axillary lymph node biopsy was negative for nodal metastasis. The tumor was estrogen receptor and progesterone receptor positive but HER-2 negative. After discussion of management options, the patient is started on tamoxifen. While on this medication, she experiences hot flashes that come and go in waves and affect her sleep significantly. Which of the following conditions is the patient also likely to experience as a result of this therapy?

- ✗ A. Decrease in bone mass (22%)
- B. Decrease in HDL level (1%)
- ✓ C. Endometrial hyperplasia (72%)
- D. Fibroadenoma of the breast (0%)
- E. Increase in LDL level (2%)

Incorrect
Correct answer
C

72%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

Selective estrogen receptor modulators	
Drugs	• Tamoxifen • Raloxifene
Mechanism of action	• Competitive inhibitor of estrogen binding • Mixed agonist/antagonist action
Indications	• Prevention of breast cancer in high-risk patients • Tamoxifen: adjuvant treatment of breast cancer

https://t.me/USMLEWorldStep1

Selective estrogen receptor modulators	
Drugs	• Tamoxifen • Raloxifene
Mechanism of action	• Competitive inhibitor of estrogen binding • Mixed agonist/antagonist action
Indications	• Prevention of breast cancer in high-risk patients • Tamoxifen: adjuvant treatment of breast cancer • Raloxifene: postmenopausal osteoporosis
Adverse effects	• Hot flashes • Venous thromboembolism • Endometrial hyperplasia & carcinoma (tamoxifen only) • Uterine sarcoma (tamoxifen only)

Tamoxifen and raloxifene are **selective estrogen receptor modulators** (SERMs). They interact with the estrogen receptor and have agonist or antagonist activity depending on the tissue. In breast tissue, tamoxifen has an anti-estrogenic effect, and it is used for adjuvant treatment of estrogen receptor-positive **breast cancer**. Tamoxifen reduces the risk of recurrent cancer as well as estrogen-dependent benign breast lesions (eg, fibroadenoma, cystic changes) **(Choice D)**.

In endometrial tissue, however, tamoxifen has a stimulatory effect and can lead to development of **endometrial hyperplasia** and endometrial cancer. This risk is not seen with raloxifene.

(Choice A) Tamoxifen and raloxifene act as partial estrogen receptor agonists in bone and can cause an increase in bone mineral density after menopause.

(Choices B and E) Tamoxifen has a favorable effect on serum lipids, with a decrease in total and LDL cholesterol and no significant change in HDL. Serum triglycerides may increase in some patients.

Educational objective:
Selective estrogen receptor modulators (eg, tamoxifen, raloxifene) are competitive inhibitors of estrogen binding to

https://t.me/USMLEWorldStep1

	• Raloxifene: postmenopausal osteoporosis
Adverse effects	• Hot flashes • Venous thromboembolism • Endometrial hyperplasia & carcinoma (tamoxifen only) • Uterine sarcoma (tamoxifen only)

Tamoxifen and raloxifene are **selective estrogen receptor modulators** (SERMs). They interact with the estrogen receptor and have agonist or antagonist activity depending on the tissue. In breast tissue, tamoxifen has an anti-estrogenic effect, and it is used for adjuvant treatment of estrogen receptor-positive **breast cancer**. Tamoxifen reduces the risk of recurrent cancer as well as estrogen-dependent benign breast lesions (eg, fibroadenoma, cystic changes) **(Choice D)**.

In endometrial tissue, however, tamoxifen has a stimulatory effect and can lead to development of **endometrial hyperplasia** and endometrial cancer. This risk is not seen with raloxifene.

(Choice A) Tamoxifen and raloxifene act as partial estrogen receptor agonists in bone and can cause an increase in bone mineral density after menopause.

(Choices B and E) Tamoxifen has a favorable effect on serum lipids, with a decrease in total and LDL cholesterol and no significant change in HDL. Serum triglycerides may increase in some patients.

Educational objective:
Selective estrogen receptor modulators (eg, tamoxifen, raloxifene) are competitive inhibitors of estrogen binding to estrogen receptors. They can have agonist or antagonist effects depending on the specific tissue. Tamoxifen has an estrogenic effect on the uterus and can cause endometrial hyperplasia and cancer.

References

- Tamoxifen treatment for breast cancer and risk of endometrial cancer: a case-control study.

Pharmacology	Endocrine, Diabetes & Metabolism	Breast cancer
Subject	System	Topic

Copyright © UWorld. All rights reserved.

https://t.me/USMLEWorldStep1

A 50-year-old man comes to the physician for a routine check-up. He has a 20-pack-year smoking history and consumes alcohol occasionally. He eats a balanced diet and consumes fried foods and red meat several times a week. He is not very active and spends much of his free time watching television and sitting at his computer. His family history is significant for hypertension in his mother and bladder cancer in his father. His blood pressure is 160/90 mm Hg and heart rate is 70/min. Laboratory testing is significant for a fasting blood glucose level of 155 mg/dL. Which of the following interventions is likely to have the greatest effect on reducing this patient's mortality risk?

- A. Annual fecal occult blood test
- B. Annual prostate-specific antigen test
- C. Daily aspirin
- D. Dietary modification
- E. Regular exercise
- F. Smoking cessation
- G. Tight glycemic control

Submit

https://t.me/USMLEWorldStep1

A 50-year-old man comes to the physician for a routine check-up. He has a 20-pack-year smoking history and consumes alcohol occasionally. He eats a balanced diet and consumes fried foods and red meat several times a week. He is not very active and spends much of his free time watching television and sitting at his computer. His family history is significant for hypertension in his mother and bladder cancer in his father. His blood pressure is 160/90 mm Hg and heart rate is 70/min. Laboratory testing is significant for a fasting blood glucose level of 155 mg/dL. Which of the following interventions is likely to have the greatest effect on reducing this patient's mortality risk?

- A. Annual fecal occult blood test (0%)
- ✕ B. Annual prostate-specific antigen test (0%)
- C. Daily aspirin (3%)
- D. Dietary modification (7%)
- E. Regular exercise (11%)
- ✓ F. Smoking cessation (67%)
- G. Tight glycemic control (8%)

Incorrect
Correct answer
F

67%
Answered correctly

03 secs
Time Spent

2023
Version

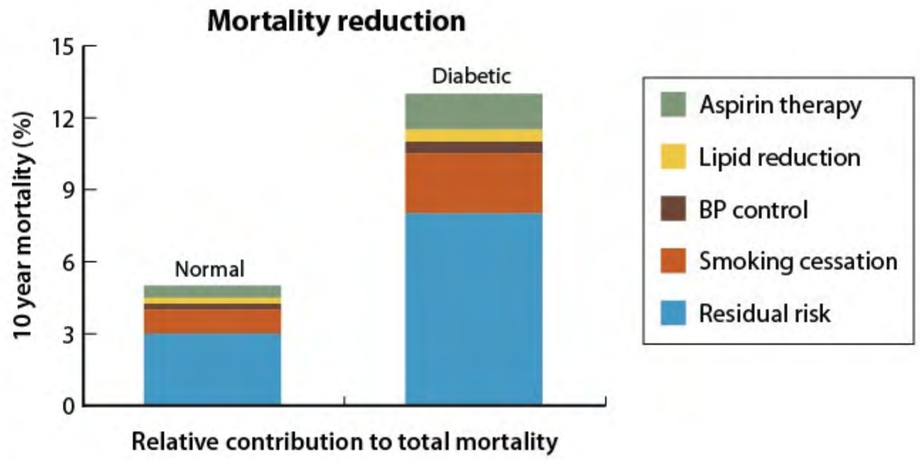
Explanation



https://t.me/USMLEWorldStep1

Mortality reduction

Exhibit Display



© USMLEWorld, LLC

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

One o
smoki
most p
effects
stroke
signifi
decrea
returns
higher
appea
develo

(Choi
detect

(Choice B) Prostate-specific antigen is increased in some patients with prostate cancer. However, annual prostate-specific antigen testing has not been shown to improve mortality from prostate cancer.

https://t.me/USMLEWorldStep1

One of the objectives for the national Healthy People 2020 initiative is to reduce the prevalence of tobacco smoking in adults from 20% in 2008 to less than 12% by 2020. Tobacco use, especially smoking, is the single most preventable cause of death and disease in the United States. In addition to its numerous direct adverse effects, tobacco smoking also substantially increases the risk for macrovascular (eg, myocardial infarction [MI], stroke) and microvascular (eg, retinopathy, nephropathy) complications of diabetes mellitus. These complications significantly increase mortality, primarily by increasing the risk of MI. The risk of MI-associated mortality begins to decrease immediately upon smoking cessation. However, it takes several tobacco-free years before the risk returns to baseline, especially in patients with a long history of smoking. In addition, smokers with diabetes have a higher likelihood of developing hypercholesterolemia, poor glycemic control, and end-stage renal disease. It appears that smoking not only worsens the complications of diabetes but also increases the likelihood of developing diabetes in the first place, thus highlighting the importance of prevention and early cessation.

(Choice A) Fecal occult blood testing screens for colorectal cancer and improves mortality through earlier detection. Even so, the mortality benefit is much lower than that achieved by smoking cessation.

(Choice B) Prostate-specific antigen is increased in some patients with prostate cancer. However, annual prostate-specific antigen testing has not been shown to improve mortality from prostate cancer.

(Choice C) Aspirin use significantly reduces the risk of death from coronary heart disease in diabetic patients, at levels similar to smoking cessation. However, when all-cause mortality is compared, smoking cessation has a greater effect on reducing mortality than daily aspirin therapy.

(Choices D, E, and G) Dietary modification and exercise reduce the risk of cardiovascular disease (to a lesser extent than smoking cessation) and help improve glycemic control in diabetic individuals. Although tight glycemic control has been shown to reduce the risk of microvascular complications from diabetes, it does not significantly improve cardiovascular or all-cause mortality.

Educational objective:
Smoking cessation is by far the most effective preventive intervention in almost all patients, and this is especially true in those with diabetes.

References

https://t.me/USMLEWorldStep1

A 21-year-old man comes to the office due to recent weight loss and fatigue. The patient is a college athlete and states, "My coach wants me to put on more weight, but I can't seem to do it. It doesn't matter how much I eat, I keep losing weight. I've been really thirsty and drinking lots of water lately too, and it's causing me to use the bathroom frequently during practice. I'm worried that I'm going to get dropped from the team if I don't get myself together." He is sexually active and has 1 lifetime partner. The patient's father was diagnosed with colon cancer at age 64. Which of the following studies would be the best next step to establish the diagnosis in this patient?

- A. Colonoscopy
- B. Hemoglobin A1c
- C. HIV testing
- D. Serum TSH level
- E. Urinalysis
- F. Urine drug screen

Submit

https://t.me/USMLEWorldStep1

A 21-year-old man comes to the office due to recent weight loss and fatigue. The patient is a college athlete and states, "My coach wants me to put on more weight, but I can't seem to do it. It doesn't matter how much I eat, I keep losing weight. I've been really thirsty and drinking lots of water lately too, and it's causing me to use the bathroom frequently during practice. I'm worried that I'm going to get dropped from the team if I don't get myself together." He is sexually active and has 1 lifetime partner. The patient's father was diagnosed with colon cancer at age 64. Which of the following studies would be the best next step to establish the diagnosis in this patient?

- A. Colonoscopy (1%)
- ✓ B. Hemoglobin A1c (62%)
- C. HIV testing (0%)
- D. Serum TSH level (12%)
- E. Urinalysis (19%)
- F. Urine drug screen (2%)

Correct

62% Answered correctly

03 secs Time Spent

2023 Version

Explanation

Type 1 diabetes mellitus	
Etiology	• Autoimmune destruction of pancreatic beta cells • **Insulin deficiency**
Signs & symptoms	• Polydipsia, polyuria • Polyphagia • Weight loss

https://t.me/USMLEWorldStep1

Type 1 diabetes mellitus	
Etiology	• Autoimmune destruction of pancreatic beta cells • **Insulin deficiency**
Signs & symptoms	• Polydipsia, polyuria • Polyphagia • Weight loss • Blurred vision • Ketoacidosis
Diagnosis	• **Fasting glucose** (≥126 mg/dL) • **Hemoglobin A1c** (≥6.5%) • Random glucose (≥200 mg/dL) • Oral glucose tolerance test

This patient's polyuria, polydipsia, fatigue, and weight loss despite increased food intake are suggestive of **type 1 diabetes mellitus**. Patients often develop these characteristic symptoms over an acute to subacute time frame and may occasionally present with diabetic ketoacidosis (nausea/vomiting, abdominal pain, decreased mental status, fruity odor to breath). Although most patients with type 1 diabetes mellitus are diagnosed before age 10, onset in adolescence and adulthood is not uncommon.

Appropriate initial tests and related diagnostic criteria for diabetes include:

- **Fasting plasma glucose ≥126 mg/dL**
- **Hemoglobin A1c ≥6.5%**
- **Random (nonfasting) glucose ≥200 mg/dL** in a patient with **symptoms** of hyperglycemia (eg, polyuria, polydipsia)
- Oral glucose tolerance test with plasma glucose ≥200 mg/dL 2 hours after glucose ingestion (preferred for diagnosis of gestational diabetes)

https://t.me/USMLEWorldStep1

	• Random glucose (≥200 mg/dL) • Oral glucose tolerance test

This patient's polyuria, polydipsia, fatigue, and weight loss despite increased food intake are suggestive of **type 1 diabetes mellitus**. Patients often develop these characteristic symptoms over an acute to subacute time frame and may occasionally present with diabetic ketoacidosis (nausea/vomiting, abdominal pain, decreased mental status, fruity odor to breath). Although most patients with type 1 diabetes mellitus are diagnosed before age 10, onset in adolescence and adulthood is not uncommon.

Appropriate initial tests and related diagnostic criteria for diabetes include:

- **Fasting plasma glucose ≥126 mg/dL**
- **Hemoglobin A1c ≥6.5%**
- **Random (nonfasting) glucose ≥200 mg/dL** in a patient with **symptoms** of hyperglycemia (eg, polyuria, polydipsia)
- Oral glucose tolerance test with plasma glucose ≥200 mg/dL 2 hours after glucose ingestion (preferred for diagnosis of gestational diabetes)

(Choice A) Colon cancer in a first-degree relative increases an individual's risk for this disease. However, because this patient's father was at an advanced age at diagnosis, the patient's risk is not significantly elevated.

(Choice C) Acute HIV presents as an acute viral syndrome with nonspecific symptoms and signs (eg, weight loss, fatigue). However, polyuria and polydipsia suggest diabetes rather than acute HIV.

(Choice D) It is possible that weight loss and polyuria are due to thyrotoxicosis, but the absence of other symptoms of thyroid disease (eg, palpitations, heat intolerance, excessive sweating) makes this less likely.

(Choice E) Acute cystitis can cause frequent urination but the total urine volume is not increased, and polydipsia and weight loss are more suggestive of diabetes mellitus. Although urinalysis can detect glucosuria, it has low sensitivity for diabetes and should not be used to confirm the diagnosis.

(Choice F) Although surreptitious drug abuse can be considered in patients with weight loss or other unexplained symptoms, a hemoglobin A1c test is more likely to be diagnostic in light of this patient's polyuria and polydipsia.

https://t.me/USMLEWorldStep1

and may occasionally present with diabetic ketoacidosis (nausea/vomiting, abdominal pain, decreased mental status, fruity odor to breath). Although most patients with type 1 diabetes mellitus are diagnosed before age 10, onset in adolescence and adulthood is not uncommon.

Appropriate initial tests and related diagnostic criteria for diabetes include:

- **Fasting plasma glucose ≥126 mg/dL**
- **Hemoglobin A1c ≥6.5%**
- **Random (nonfasting) glucose ≥200 mg/dL** in a patient with **symptoms** of hyperglycemia (eg, polyuria, polydipsia)
- Oral glucose tolerance test with plasma glucose ≥200 mg/dL 2 hours after glucose ingestion (preferred for diagnosis of gestational diabetes)

(Choice A) Colon cancer in a first-degree relative increases an individual's risk for this disease. However, because this patient's father was at an advanced age at diagnosis, the patient's risk is not significantly elevated.

(Choice C) Acute HIV presents as an acute viral syndrome with nonspecific symptoms and signs (eg, weight loss, fatigue). However, polyuria and polydipsia suggest diabetes rather than acute HIV.

(Choice D) It is possible that weight loss and polyuria are due to thyrotoxicosis, but the absence of other symptoms of thyroid disease (eg, palpitations, heat intolerance, excessive sweating) makes this less likely.

(Choice E) Acute cystitis can cause frequent urination but the total urine volume is not increased, and polydipsia and weight loss are more suggestive of diabetes mellitus. Although urinalysis can detect glucosuria, it has low sensitivity for diabetes and should not be used to confirm the diagnosis.

(Choice F) Although surreptitious drug abuse can be considered in patients with weight loss or other unexplained symptoms, a hemoglobin A1c test is more likely to be diagnostic in light of this patient's polyuria and polydipsia.

Educational objective:
Type 1 diabetes mellitus typically presents subacutely with polyuria and polydipsia accompanied by fatigue and weight loss. The diagnosis can be confirmed with a fasting blood glucose or hemoglobin A1c measurement.

References

https://t.me/USMLEWorldStep1

A 44-year-old man comes to the clinic due to increasing fatigue, trouble sleeping, and palpitations. He has lost 9 kg (20 lb) over the last year despite eating well. The patient says he is under a lot of pressure at work but cannot think of any other precipitating factors for his insomnia. He has no other medical problems and takes no medications. The patient does not use tobacco, alcohol, or recreational drugs. His mother has a history of a thyroid problem. Blood pressure is 140/80 mm Hg and pulse is 108/min. On physical examination, the thyroid is diffusely enlarged. His serum free thyroxine level is elevated and TSH level is decreased. He is found to have a positive assay for thyrotropin receptor antibodies. Compared to other forms of thyroid disease, which of the following findings would be most specific for this patient's underlying pathophysiologic process?

- A. Atrial fibrillation
- B. Decreased bone mineral density
- C. Heat intolerance
- D. Skin thickening and induration over the shin
- E. Tremor of the outstretched hands

Submit

https://t.me/USMLEWorldStep1

A 44-year-old man comes to the clinic due to increasing fatigue, trouble sleeping, and palpitations. He has lost 9 kg (20 lb) over the last year despite eating well. The patient says he is under a lot of pressure at work but cannot think of any other precipitating factors for his insomnia. He has no other medical problems and takes no medications. The patient does not use tobacco, alcohol, or recreational drugs. His mother has a history of a thyroid problem. Blood pressure is 140/80 mm Hg and pulse is 108/min. On physical examination, the thyroid is diffusely enlarged. His serum free thyroxine level is elevated and TSH level is decreased. He is found to have a positive assay for thyrotropin receptor antibodies. Compared to other forms of thyroid disease, which of the following findings would be most specific for this patient's underlying pathophysiologic process?

- A. Atrial fibrillation (11%)
- ✗ B. Decreased bone mineral density (6%)
- C. Heat intolerance (17%)
- ✓ D. Skin thickening and induration over the shin (53%)
- E. Tremor of the outstretched hands (10%)

Incorrect
Correct answer
D

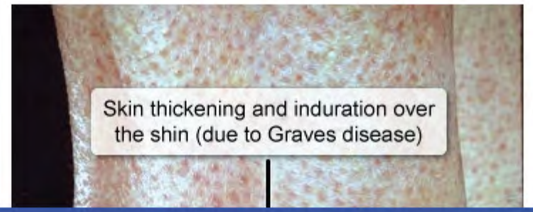
53%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

Pretibial myxedema



https://t.me/USMLEWorldStep1

A 44-year-old man comes to the clinic due to increasing fatigue, trouble sleeping, and palpitations. He has lost 9 kg (20
think c
medica
thyroid
diffuse
positiv
followi

Incc
Corre
D

Expl

Exhibit Display

Pretibial myxedema



©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

©UWorld

This patient has **symptomatic hyperthyroidism** with elevated serum free thyroxine and suppressed TSH levels. The most common cause of hyperthyroidism is Graves disease, however, hyperthyroidism can also be due to other processes such as toxic adenoma, toxic multinodular goiter, and thyroiditis.

This patient's positive serum assay for **thyrotropin receptor antibodies** (TRAb) confirms the diagnosis of **Graves disease**. TRAb bind and activate the TSH receptor, causing increased release of thyroid hormone by the thyroid gland, which is responsible for the general symptoms of hyperthyroidism (eg, fatigue, palpitations, weight loss, and insomnia).

The TSH receptor is also present on fibroblasts and adipocytes in addition to thyroid epithelial cells. **Thyroid dermopathy** is caused by stimulation of fibroblasts by TRAb, leading to excess production of glycosaminoglycans and adipogenesis. This leads to induration and thickening of the skin over the shins (**pretibial myxedema**). Graves ophthalmopathy occurs in a similar manner, with expansion of the retro-orbital tissues displacing the globe forward (proptosis). Because these processes are directly related to TRAb, they have a **high specificity** for Graves disease.

(Choices A, B, C, and E) Hyperthyroidism also causes a hypermetabolic/hyperadrenergic state that can present with heat intolerance, tremor, lid lag, tachycardia, or atrial fibrillation. In addition, increased bone turnover can lead to osteoporosis and increased fracture risk. However, these findings are not mediated by TRAb and can be seen in hyperthyroidism of any cause (eg, thyroiditis, toxic multinodular goiter).

Educational objective:
Pretibial myxedema and Graves ophthalmopathy are specific features of Graves disease. They are caused by an autoimmune response directed against the TSH receptor that results in the accumulation of glycosaminoglycans within the affected tissues.

References

- Thyroid dermopathy and acropachy.

Pathophysiology	Endocrine, Diabetes & Metabolism	Hyperthyroidism
Subject	System	Topic

https://t.me/USMLEWorldStep1

©UWorld

This patient has **symptomatic hyperthyroidism** with elevated serum free thyroxine and suppressed TSH levels.

The m

proces

This p

diseas

gland,

insom

The TS

dermo

and ac

Grave

forwar

Grave

(Choi

with h

to oste

in hyp

Educa

Pretibi

autoim

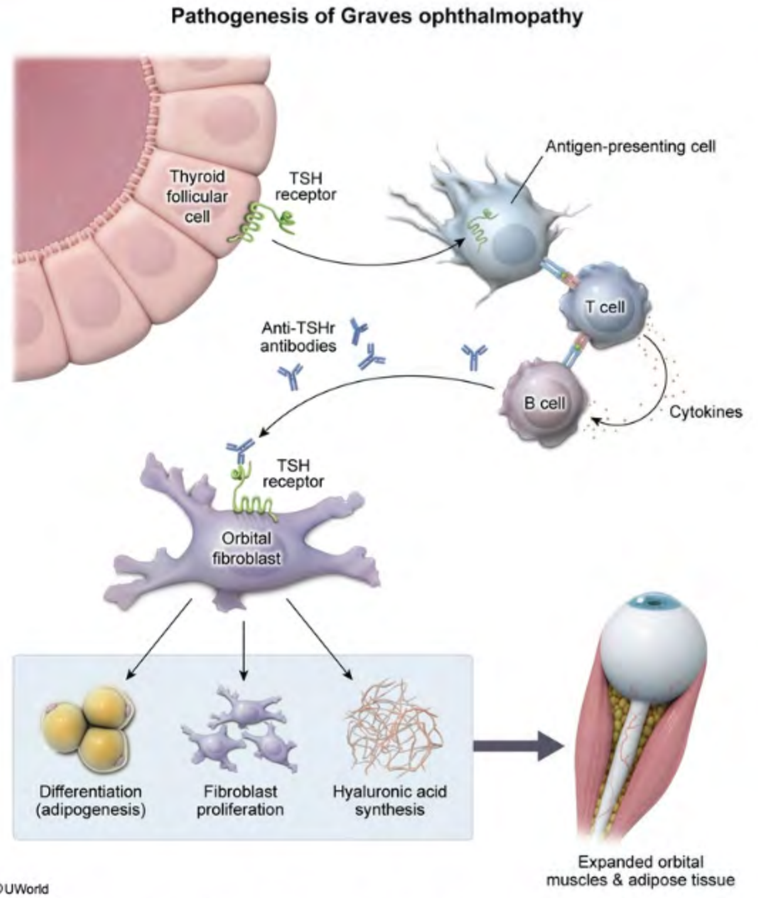
within

Refere

- Thy

Pathophysiology | Endocrine, Diabetes & Metabolism | Hyperthyroidism
Subject | System | Topic

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

©UWorld

This patient has **symptomatic hyperthyroidism** with elevated serum free thyroxine and suppressed TSH levels.

The m

proces

This p

diseas

gland,

insom

The TS

dermo

and ac

Grave

forwar

Grave

(Choi

with h

to oste

in hyp

Educa

Pretibi

autoim

within

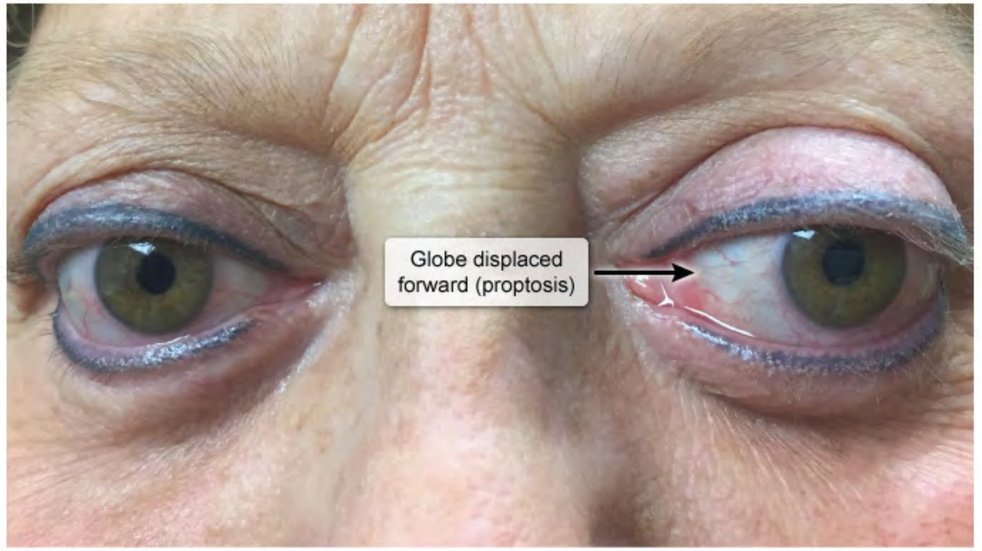
Refere

- Thy

Pathophysiology | Endocrine, Diabetes & Metabolism | Hyperthyroidism
Subject | System | Topic

Exhibit Display

Graves ophthalmopathy



©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

A 58-year-old man comes to the office for evaluation of a foot wound. The patient noticed a small ulcer on the bottom of his right foot a week ago but recalls no significant foot injury. He has been applying antiseptics, but the wound has failed to heal. The patient has a 15-year history of type 2 diabetes mellitus and is nonadherent to medical therapy. He has smoked a pack of cigarettes daily for 20 years. Temperature is 37.1 C (98.8 F), blood pressure is 140/80 mm Hg, and pulse is 72/min. Right lower extremity examination shows a 1-cm (0.39-in) plantar ulcer under the first metatarsal head. There are no other lesions, and the tibial and dorsalis pedis pulses are normal. Which of the following is the strongest contributing factor underlying the development of this patient's foot ulcer?

- A. Atherosclerotic disease
- B. Bacterial infection
- C. Irritant dermatitis
- D. Sensory impairment
- E. Systemic vasculitis
- F. Venous insufficiency

Submit

https://t.me/USMLEWorldStep1

A 58-year-old man comes to the office for evaluation of a foot wound. The patient noticed a small ulcer on the bottom of his right foot a week ago but recalls no significant foot injury. He has been applying antiseptics, but the wound has failed to heal. The patient has a 15-year history of type 2 diabetes mellitus and is nonadherent to medical therapy. He has smoked a pack of cigarettes daily for 20 years. Temperature is 37.1 C (98.8 F), blood pressure is 140/80 mm Hg, and pulse is 72/min. Right lower extremity examination shows a 1-cm (0.39-in) plantar ulcer under the first metatarsal head. There are no other lesions, and the tibial and dorsalis pedis pulses are normal. Which of the following is the strongest contributing factor underlying the development of this patient's foot ulcer?

- A. Atherosclerotic disease (13%)
- ✕ B. Bacterial infection (2%)
- C. Irritant dermatitis (0%)
- ✓ D. Sensory impairment (68%)
- E. Systemic vasculitis (5%)
- F. Venous insufficiency (8%)

Incorrect
Correct answer
D

68%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

Lower extremity ulcers			
	Arterial insufficiency	**Venous insufficiency**	**Neuropathic**
Common location	Tips of toes, malleoli	Medial tibia	Bony prominences, plantar surfaces

https://t.me/USMLEWorldStep1

Lower extremity ulcers			
	Arterial insufficiency	**Venous insufficiency**	**Neuropathic**
Common location	Tips of toes, malleoli	Medial tibia	Bony prominences, plantar surfaces
Clinical features	Sharply demarcated, pale base; deep	Irregular, shallow, erythematous base with granulation tissue & exudate	Sharply demarcated, erythematous base
Pain	Very painful	Moderate pain	None
Skin changes	Hairless, shiny, cold	Brown/hyperpigmentation, erythema, thickened skin	Dry, scaly, calloused
Pulses	Decreased/absent	Present	Present
Associated conditions	Smoking, hypertension, atherosclerosis	Deep vein thrombosis, varicose veins, pregnancy, increased age	Diabetes mellitus, other peripheral neuropathy
Treatment	Revascularization, antiplatelet agents	Compression, elevation	Pressure offloading

This patient has a plantar ulcer under the first metatarsal head. In a patient with chronic, poorly controlled **diabetes mellitus**, this is likely a **neuropathic ulcer** due to underlying peripheral **sensory neuropathy**. Chronic hyperglycemia promotes nerve injury and impairs nerve repair in distal sensory fibers, causing decreased sensation of pain, pressure, and proprioception.

Loss of these protective senses can cause individuals to not recognize an injury due to minor trauma, friction, or **pressure**. Areas that are particularly susceptible are points of localized pressure created by a shoe or weight-bearing bones of the foot (eg, plantar surface of the **first metatarsal head**). A wound in this area often goes unnoticed (due to lack of pain sensation and being hidden by socks or shoes) and can develop into a nonhealing

https://t.me/USMLEWorldStep1

This patient has a plantar ulcer under the first metatarsal head. In a patient with chronic, poorly controlled **diabetes mellitus**, this is likely a **neuropathic ulcer** due to underlying peripheral **sensory neuropathy**. Chronic hyperglycemia promotes nerve injury and impairs nerve repair in distal sensory fibers, causing decreased sensation of pain, pressure, and proprioception.

Loss of these protective senses can cause individuals to not recognize an injury due to minor trauma, friction, or **pressure**. Areas that are particularly susceptible are points of localized pressure created by a shoe or weight-bearing bones of the foot (eg, plantar surface of the **first metatarsal head**). A wound in this area often goes unnoticed (due to lack of pain sensation and being hidden by socks or shoes) and can develop into a nonhealing foot ulcer.

Loss of proprioception and an increase in ligamentous laxity can also cause chronic pressure-induced joint/skin damage in the feet of patients with diabetic neuropathy, which can lead to calluses or foot deformities (eg, Charcot foot, hammer toe).

(Choice A) Although diabetic patients (especially those who smoke) often have comorbid arterial insufficiency, arterial ulcers are typically painful, sharply demarcated, and located at the tips of the toes. This patient has full distal pulses, which makes clinically significant atherosclerotic disease unlikely to be the primary cause of the ulcer.

(Choice B) Bacterial infection may delay ulcer healing, especially if there is underlying osteomyelitis, but it is not the inciting cause of neuropathic ulcers. In addition, although diabetic ulcers are often colonized by bacteria, this patient has no fever, erythema, or purulent drainage to suggest serious infection.

(Choice C) Irritant contact dermatitis presents with pruritic or painful erythema in areas of exposed skin (eg, hands). It can occasionally cause small vesicles or fissures, but ulcers are not typical.

(Choice E) Systemic vasculitic disorders (eg, polyarteritis nodosa) are an uncommon cause of skin ulcers. Vasculitic ulcers are usually painful and associated with other skin (eg, purpura, nodules) and systemic (eg, fever, fatigue) symptoms.

(Choice F) Ulcers caused by venous insufficiency are most common over the tibias or proximal to the medial malleolus. They present as irregular ulcerations in the setting of stasis dermatitis and/or varicose veins.

Educational objective:

https://t.me/USMLEWorldStep1

sensation of pain, pressure, and proprioception.

Loss of these protective senses can cause individuals to not recognize an injury due to minor trauma, friction, or **pressure**. Areas that are particularly susceptible are points of localized pressure created by a shoe or weight-bearing bones of the foot (eg, plantar surface of the **first metatarsal head**). A wound in this area often goes unnoticed (due to lack of pain sensation and being hidden by socks or shoes) and can develop into a nonhealing foot ulcer.

Loss of proprioception and an increase in ligamentous laxity can also cause chronic pressure-induced joint/skin damage in the feet of patients with diabetic neuropathy, which can lead to calluses or foot deformities (eg, Charcot foot, hammer toe).

(Choice A) Although diabetic patients (especially those who smoke) often have comorbid arterial insufficiency, arterial ulcers are typically painful, sharply demarcated, and located at the tips of the toes. This patient has full distal pulses, which makes clinically significant atherosclerotic disease unlikely to be the primary cause of the ulcer.

(Choice B) Bacterial infection may delay ulcer healing, especially if there is underlying osteomyelitis, but it is not the inciting cause of neuropathic ulcers. In addition, although diabetic ulcers are often colonized by bacteria, this patient has no fever, erythema, or purulent drainage to suggest serious infection.

(Choice C) Irritant contact dermatitis presents with pruritic or painful erythema in areas of exposed skin (eg, hands). It can occasionally cause small vesicles or fissures, but ulcers are not typical.

(Choice E) Systemic vasculitic disorders (eg, polyarteritis nodosa) are an uncommon cause of skin ulcers. Vasculitic ulcers are usually painful and associated with other skin (eg, purpura, nodules) and systemic (eg, fever, fatigue) symptoms.

(Choice F) Ulcers caused by venous insufficiency are most common over the tibias or proximal to the medial malleolus. They present as irregular ulcerations in the setting of stasis dermatitis and/or varicose veins.

Educational objective:
Neuropathic foot ulcers can occur in diabetic patients when loss of pain sensation and proprioception delays recognition of injury due to trauma, friction, or sustained pressure (on plantar surface of foot bones). The risk is greatest in patients with longstanding diabetes who have poor glycemic control.

https://t.me/USMLEWorldStep1

conditions	atherosclerosis	increased age	peripheral neuropathy

Exhibit Display

Neuropathic ulcer



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

This p
diabet
hyperg
sensat

Loss c
press
bearin
unnoti
foot ul

Loss c
damag
foot, h

(Choi
arteria
distal p

(Choi
the inc
patien

(Choi
hands

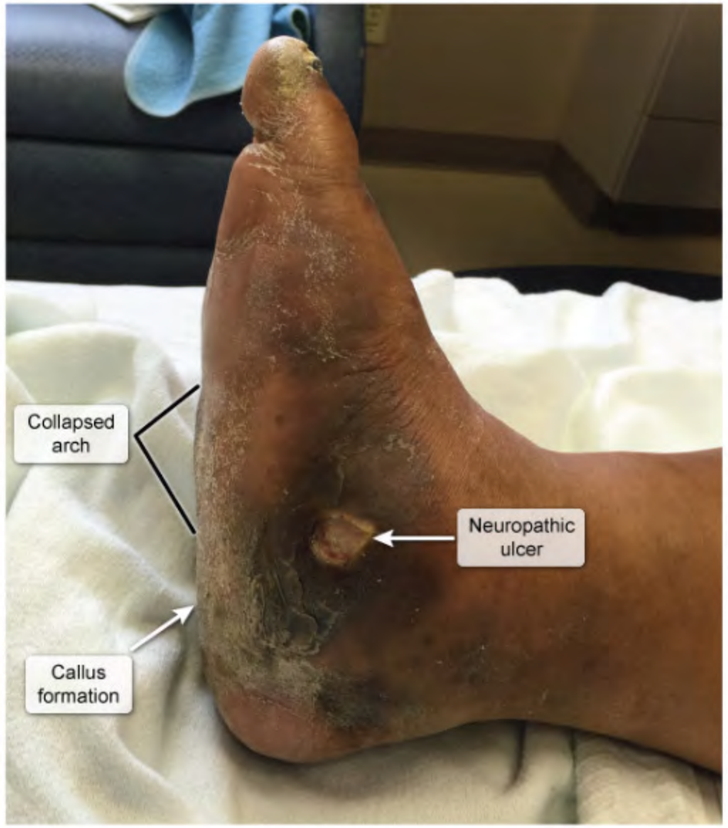
(Choi
Vasculitic ulcers are usually painful and associated with other skin (eg, purpura, nodules) and systemic (eg, fever, fatigue) symptoms

https://t.me/USMLEWorldStep1

conditions	atherosclerosis	increased age	peripheral neuropathy

Exhibit Display

Chronic neuropathic (Charcot) arthropathy



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

This p
diabet
hyperg
sensat

Loss c
press
bearin
unnoti
foot ul

Loss c
damag
foot, h

(Choi
arteria
distal p

(Choi
the inc
patien

(Choi
hands

(Choi
Vasculitic ulcers are usually painful and associated with other skin (eg, purpura, nodules) and systemic (eg, fever, fatigue) symptoms

https://t.me/USMLEWorldStep1

conditions	atherosclerosis	increased age	peripheral neuropathy

Exhibit Display

This p
diabet
hyperg
sensat

Loss o
press
bearin
unnoti
foot ul

Loss o
damag
foot, h

(Choi
arteria
distal p

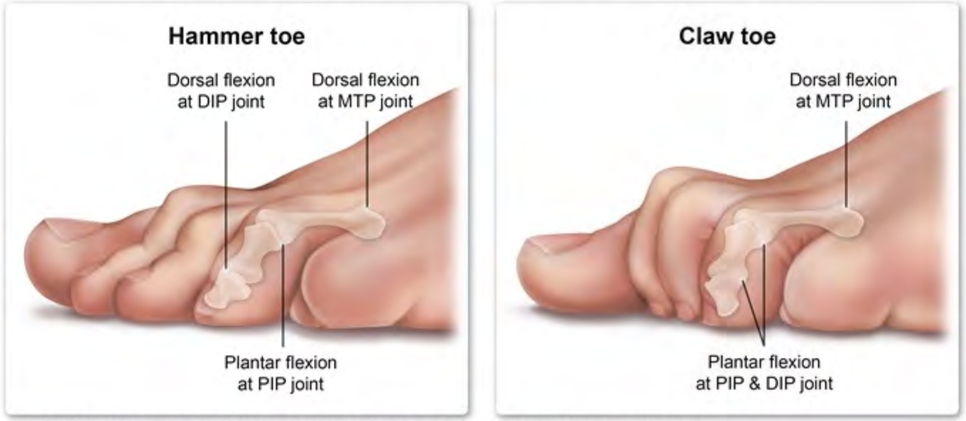
(Choi
the inc
patien

(Choi
hands

(Choi

Vasculitic ulcers are usually painful and associated with other skin (eg, purpura, nodules) and systemic (eg, fever, fatigue) symptoms

Hammer & claw toe deformities



DIP = distal interphalangeal; **MTP** = metatarsophalangeal; **PIP** = proximal interphalangeal.
©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

sensation of pain, pressure, and proprioception.

Loss o
press
bearin
unnoti
foot ul

Loss o
damag
foot, h

(Choi
arteria
distal p

(Choi
the inc
patien

(Choi
hands

(Choi
Vascu
fatigue

(Choi
malleo

Educa
Neuro
recognition of injury due to trauma, friction, or sustained pressure (on plantar surface of foot bones). The risk is greatest in patients with longstanding diabetes who have poor glycemic control

Exhibit Display

Irritant contact dermatitis



©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

bearing bones of the foot (eg, plantar surface of the **first metatarsal head**). A wound in this area often goes unnoti
foot ul

Loss c
damag
foot, h

(Choi
arteria
distal

(Choi
the inc
patien

(Choi
hands

(Choi
Vascu
fatigue

(Choi
malleo

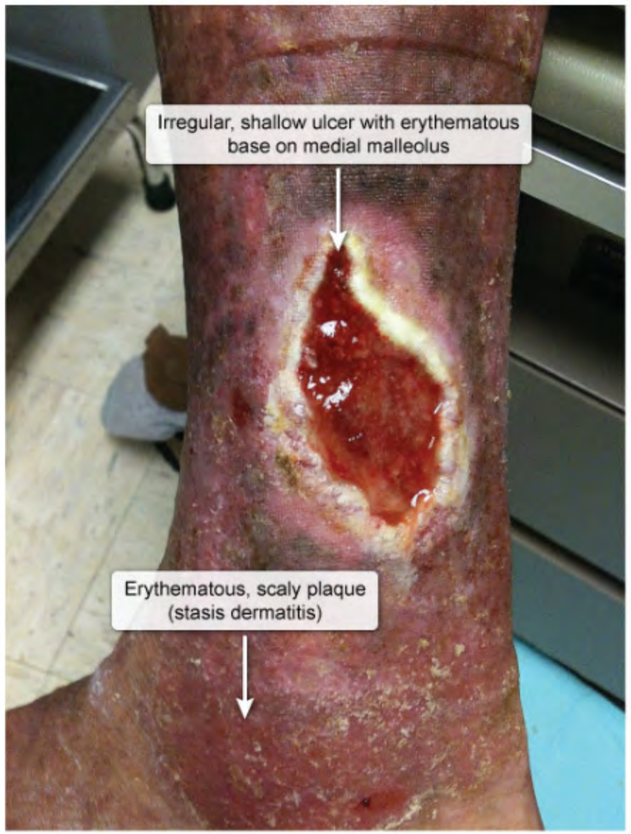
Educa
Neuro
recogn
greate

Refere

- The diabetic foot.

Exhibit Display

Venous insufficiency ulcer



©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

A 50-year-old woman comes to the office concerned that her menstrual periods have stopped. She took oral contraceptive pills for the past 17 years, which she discontinued 3 months ago, and her menses have not returned. The patient had one spontaneous abortion at age 27 and otherwise has never been pregnant. She is monogamous with her husband, and they have sexual intercourse regularly. The patient has some vaginal dryness but no pain or discomfort with intercourse. BMI is 21 kg/m^2 and vital signs are normal. Speculum examination shows a normal vaginal mucosa and cervix. Bimanual examination shows a normal uterus and ovaries. Urine pregnancy test is negative. Which of the following hormones is most likely elevated in this patient?

- A. β-hCG
- B. Estradiol
- C. FSH
- D. Progesterone
- E. Prolactin

Submit

https://t.me/USMLEWorldStep1

A 50-year-old woman comes to the office concerned that her menstrual periods have stopped. She took oral contraceptive pills for the past 17 years, which she discontinued 3 months ago, and her menses have not returned. The patient had one spontaneous abortion at age 27 and otherwise has never been pregnant. She is monogamous with her husband, and they have sexual intercourse regularly. The patient has some vaginal dryness but no pain or discomfort with intercourse. BMI is 21 kg/m^2 and vital signs are normal. Speculum examination shows a normal vaginal mucosa and cervix. Bimanual examination shows a normal uterus and ovaries. Urine pregnancy test is negative. Which of the following hormones is most likely elevated in this patient?

- A. β-hCG (0%)
- ✗ B. Estradiol (5%)
- ✓ C. FSH (74%)
- D. Progesterone (11%)
- E. Prolactin (7%)

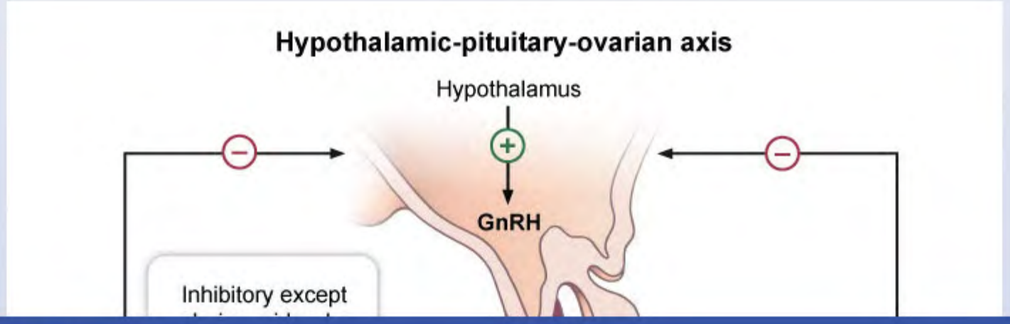
Incorrect
Correct answer
C

74%
Answered correctly

03 secs
Time Spent

2023
Version

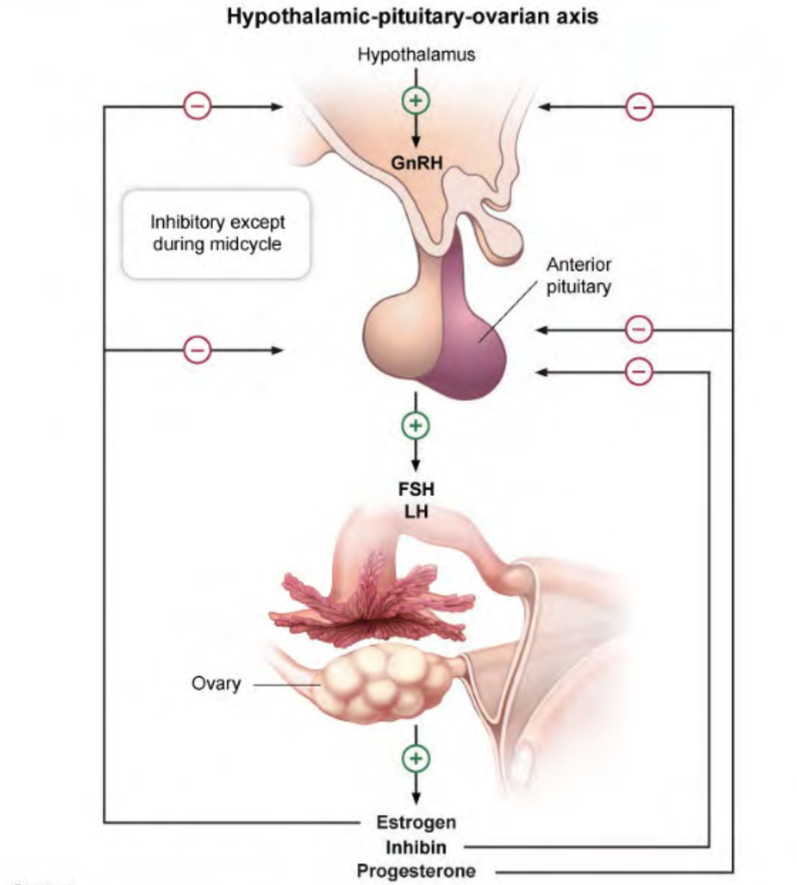
Explanation



https://t.me/USMLEWorldStep1

A 50-year-old woman comes to the office concerned that her menstrual periods have stopped. She took oral contra
returne
monog
but no
shows
pregna

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Inhibitory except

https://t.me/USMLEWorldStep1

Menopause is defined by the permanent cessation of menses for **12 months** and is a normal event of aging caused by exhaustion of ovarian follicles. The mean age of menopause in the United States is 51. Ovarian failure before age 35 is considered premature. During the menopausal transition, **FSH levels increase** due to resistant ovarian follicles and lack of feedback from inhibin. Absence of menstrual cycles with associated **hypoestrogenic symptoms** (eg, hot flashes, vaginal dryness) is highly suggestive of menopause. Menopause is typically diagnosed clinically. However, if the diagnosis is unclear, an elevated serum FSH level can be used for diagnosis as it is a reliable early indicator.

Cyclic and continuous oral contraceptive (OC) regimens are not associated with irregular menses or amenorrhea, and premenopausal patients who stop taking OCs should expect spontaneous return of menses. This patient's age and vaginal dryness make menopausal transition the most likely cause of amenorrhea. OCs may mask vasomotor symptoms that are typical of menopausal transition, and the patient was likely having iatrogenic withdrawal bleeding.

(Choice A) A urine pregnancy test should be performed for any female of reproductive age with amenorrhea. A negative test is a reliable indicator that the patient is not pregnant. Serum β-hCG testing is indicated in cases when the absolute value of the β-hCG would aid in diagnosis and treatment, such as in ectopic or molar pregnancies.

(Choices B and D) Estradiol and progesterone levels gradually decrease during the menopausal transition due to decreasing ovarian function. Serum estradiol measurement is not a reliable indicator of menopause due to typical fluctuations and gradual decline. After menopause, estrone is produced outside the ovaries and replaces estradiol as the predominant circulating estrogen.

(Choice E) Serum prolactin levels are much less significantly changed during menopause than are FSH levels. Amenorrhea due to a prolactinoma would be diagnosed by detecting an elevated prolactin level. Additional symptoms can include galactorrhea and headache, which this patient does not have.

Educational objective:
Menopause occurs on average at age 51 and is diagnosable retrospectively after 12 months of amenorrhea. An elevated serum FSH level confirms the diagnosis.

References

https://t.me/USMLEWorldStep1

A 55-year-old man comes to the emergency department due to progressive weakness and lethargy. Over the past 3 months, he has had excessive thirst, frequent urination, and an unintentional 5-kg (11-lb) weight loss. The patient has not seen a physician in several years. His parents have type 2 diabetes mellitus. Blood pressure is 108/60 mm Hg and pulse is 98/min. BMI is 38 kg/m^2. Physical examination shows dry mucous membranes and poor skin turgor. Laboratory testing reveals a blood glucose concentration of 600 mg/dL. Serum beta-hydroxybutyrate is normal and hemoglobin A1c is 14%. The patient is admitted for intravenous fluids and insulin infusion. The next day, his symptoms and blood glucose significantly improve. In preparation for discharge, the insulin infusion is changed to a subcutaneous regimen that mimics the physiologic pattern of insulin release. This patient's insulin therapy was most likely transitioned to which of the following regimens?

- A. Insulin aspart before each meal
- B. Insulin detemir twice daily
- C. Insulin glargine once daily
- D. Insulin glargine once daily plus insulin lispro before each meal
- E. NPH insulin premixed with regular insulin given twice daily

Submit

https://t.me/USMLEWorldStep1

A 55-year-old man comes to the emergency department due to progressive weakness and lethargy. Over the past 3 months, he has had excessive thirst, frequent urination, and an unintentional 5-kg (11-lb) weight loss. The patient has not seen a physician in several years. His parents have type 2 diabetes mellitus. Blood pressure is 108/60 mm Hg and pulse is 98/min. BMI is 38 kg/m^2. Physical examination shows dry mucous membranes and poor skin turgor. Laboratory testing reveals a blood glucose concentration of 600 mg/dL. Serum beta-hydroxybutyrate is normal and hemoglobin A1c is 14%. The patient is admitted for intravenous fluids and insulin infusion. The next day, his symptoms and blood glucose significantly improve. In preparation for discharge, the insulin infusion is changed to a subcutaneous regimen that mimics the physiologic pattern of insulin release. This patient's insulin therapy was most likely transitioned to which of the following regimens?

- A. Insulin aspart before each meal (19%)
- ✕ B. Insulin detemir twice daily (1%)
- C. Insulin glargine once daily (4%)
- ✓ D. Insulin glargine once daily plus insulin lispro before each meal (62%)
- E. NPH insulin premixed with regular insulin given twice daily (11%)

Incorrect
Correct answer
D

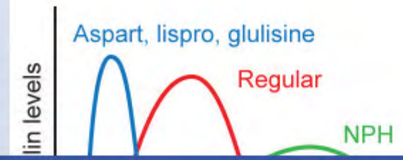
62%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

Pharmacokinetic profiles of common insulin preparations

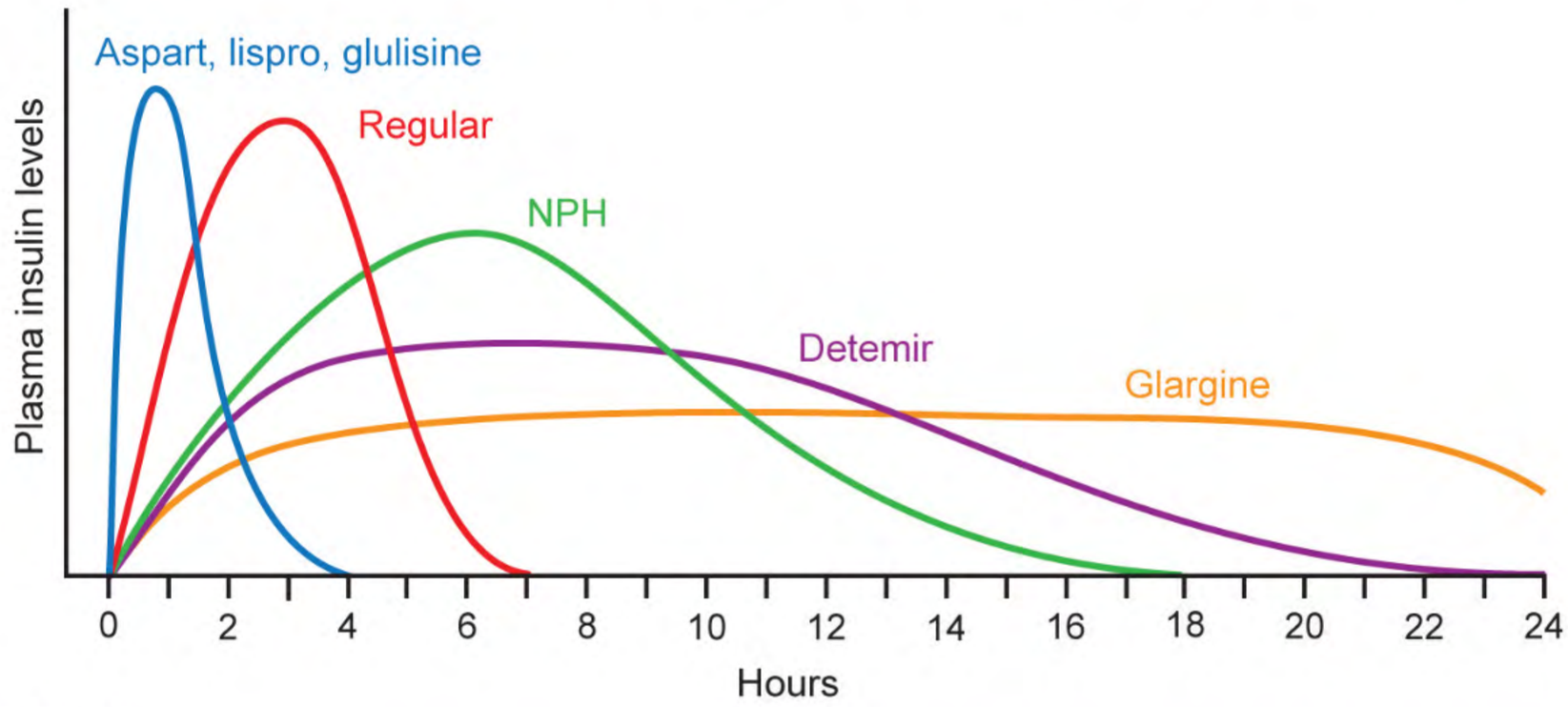


https://t.me/USMLEWorldStep1

A 55-year-old man comes to the emergency department due to progressive weakness and lethargy. Over the past
3 mon
patien
108/60
poor s
hydrox
infusic
insulin
patien

Exhibit Display

Pharmacokinetic profiles of common insulin preparations



©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

This patient has an elevated hemoglobin A1c, confirming a diagnosis of **type 2 diabetes mellitus**; he has altered mentation (eg, lethargy), dehydration (eg, dry mucous membranes), and severe hyperglycemia that is consistent with a **hyperosmolar hyperglycemic state**. After acute management (eg, intravenous fluids and insulin infusion), he needs to transition to chronic (subcutaneous) insulin therapy.

A variety of commercial insulin analogues with different pharmacokinetics are available; the ideal regimen mimics normal insulin secretion using separate injections of the following:

- **Long-acting insulins** (eg, **glargine**) mimic continuous, steady-level **basal** insulin secretion by the pancreas that suppresses hepatic gluconeogenesis; they have an extended duration of action and **little or no peak** effect. They are typically given **once daily** and are used to control fasting hyperglycemia that is attributable to inappropriate hepatic gluconeogenesis.
- **Rapid-acting insulins** (eg, lispro, aspart) mimic rapid-onset, short-lived **postprandial** insulin surges in response to meals; they **peak** and are cleared quickly. They are given multiple times daily, just before each meal, so that the peak effect coincides with postprandial glucose surges.

(Choice A) Insulin aspart alone can replicate postprandial insulin secretion but does not provide a basal insulin effect.

(Choices B and C) Insulins detemir and glargine are long-acting basal insulins without significant peak effects; because of detemir's shorter duration of action (ie, <24 hr), it is sometimes given twice daily to ensure 24-hour coverage. These medications do not treat postprandial hyperglycemia.

(Choice E) NPH is an intermediate-acting insulin; it can be used as a basal insulin if given twice daily to provide 24-hour coverage. Unlike physiologic basal insulin secretions, NPH has a significant peak effect that increases the risk for hypoglycemia. In addition, premixing with regular insulin does not easily allow for premeal bolus adjustments. Therefore, a combined formulation of NPH and regular insulin (usually in a 70/30 ratio) is less representative of physiologic insulin secretion compared to separate injections of basal and rapid-acting premeal insulin.

Educational objective:
Physiologic insulin secretion can be approximated by separate administrations of long-acting and rapid-acting

https://t.me/USMLEWorldStep1

he needs to transition to chronic (subcutaneous) insulin therapy.

A variety of commercial insulin analogues with different pharmacokinetics are available; the ideal regimen mimics normal insulin secretion using separate injections of the following:

- **Long-acting insulins** (eg, **glargine**) mimic continuous, steady-level **basal** insulin secretion by the pancreas that suppresses hepatic gluconeogenesis; they have an extended duration of action and **little or no peak** effect. They are typically given **once daily** and are used to control fasting hyperglycemia that is attributable to inappropriate hepatic gluconeogenesis.
- **Rapid-acting insulins** (eg, lispro, aspart) mimic rapid-onset, short-lived **postprandial** insulin surges in response to meals; they **peak** and are cleared quickly. They are given multiple times daily, just before each meal, so that the peak effect coincides with postprandial glucose surges.

(Choice A) Insulin aspart alone can replicate postprandial insulin secretion but does not provide a basal insulin effect.

(Choices B and C) Insulins detemir and glargine are long-acting basal insulins without significant peak effects; because of detemir's shorter duration of action (ie, <24 hr), it is sometimes given twice daily to ensure 24-hour coverage. These medications do not treat postprandial hyperglycemia.

(Choice E) NPH is an intermediate-acting insulin; it can be used as a basal insulin if given twice daily to provide 24-hour coverage. Unlike physiologic basal insulin secretions, NPH has a significant peak effect that increases the risk for hypoglycemia. In addition, premixing with regular insulin does not easily allow for premeal bolus adjustments. Therefore, a combined formulation of NPH and regular insulin (usually in a 70/30 ratio) is less representative of physiologic insulin secretion compared to separate injections of basal and rapid-acting premeal insulin.

Educational objective:
Physiologic insulin secretion can be approximated by separate administrations of long-acting and rapid-acting insulin analogues. Long-acting preparations (eg, glargine) replicate basal insulin secretion, whereas premeal, rapid-acting insulin (eg, lispro) replicates meal-related insulin surges.

References

https://t.me/USMLEWorldStep1

A 72-year-old woman is brought to the emergency department after lying on the floor in her home for the past 2 days. The patient's neighbor called police after phone calls were not answered and no one opened the door. She was found awake on the bathroom floor lying in feces and urine. The patient says she fell and injured her right hip and was unable to get up to call for help. She did not eat or drink anything during that time. On examination, the patient appears dehydrated and has right hip tenderness. Laboratory studies show serum glucose of 72 mg/dL and positive urine ketones. Radiographs of the right hip show a right femoral neck fracture. Increased activity of which of the following enzymes is most likely contributing to both the serum and urine laboratory findings?

- A. Glycogen phosphorylase
- B. Hormone-sensitive lipase
- C. Lipoprotein lipase
- D. Mitochondrial HMG CoA synthase
- E. Phosphofructokinase-1

Submit

https://t.me/USMLEWorldStep1

A 72-year-old woman is brought to the emergency department after lying on the floor in her home for the past 2 days. The patient's neighbor called police after phone calls were not answered and no one opened the door. She was found awake on the bathroom floor lying in feces and urine. The patient says she fell and injured her right hip and was unable to get up to call for help. She did not eat or drink anything during that time. On examination, the patient appears dehydrated and has right hip tenderness. Laboratory studies show serum glucose of 72 mg/dL and positive urine ketones. Radiographs of the right hip show a right femoral neck fracture. Increased activity of which of the following enzymes is most likely contributing to both the serum and urine laboratory findings?

- ✗ A. Glycogen phosphorylase (17%)
- ✓ B. Hormone-sensitive lipase (40%)
- C. Lipoprotein lipase (11%)
- D. Mitochondrial HMG CoA synthase (20%)
- E. Phosphofructokinase-1 (10%)

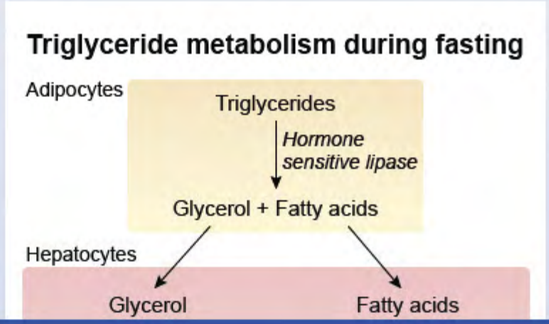
Incorrect
Correct answer
B

40%
Answered correctly

04 secs
Time Spent

2023
Version

Explanation



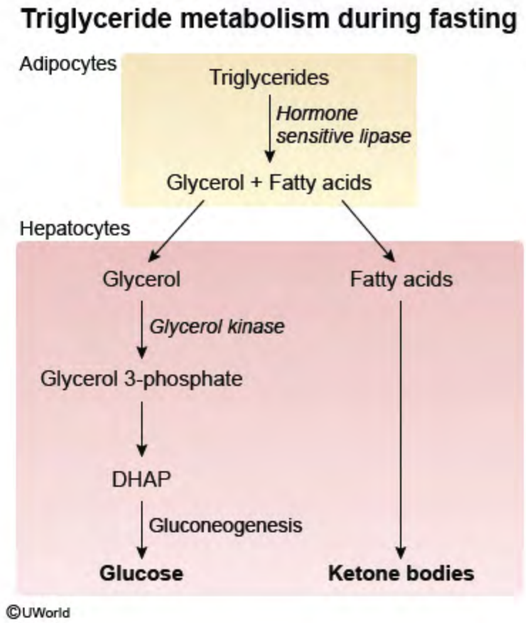
https://t.me/USMLEWorldStep1

A 72-year-old woman is brought to the emergency department after lying on the floor in her home for the past 2 days.
was fo
and w
patien
and p
which

Inco
Corre
B

Expl

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Glycerol
Fatty acids

https://t.me/USMLEWorldStep1

This patient's laboratory studies show the presence of ketones in the urine and maintenance of fasting blood glucose values in the low-normal range despite prolonged fasting.

Hormone-sensitive lipase (HSL) is an enzyme found in adipose tissue that catalyzes the mobilization of stored triglycerides into **free fatty acids** (FFAs) and **glycerol**. HSL is activated in response to stress hormones (eg, catecholamines, glucagon, ACTH), whereas it is inhibited by the release of insulin. The stress hormones stimulate Gs protein-coupled receptors on adipocytes, leading to increased cAMP production and activation of protein kinase A (PKA). Finally, PKA phosphorylates and activates HSL, stimulating lipolysis.

FFAs and glycerol released into the circulation can be taken up by the liver, where the glycerol is used primarily as a carbon source for **gluconeogenesis**. The liver oxidizes the FFAs to acetyl-coA, which can then be further metabolized to **ketone bodies** (eg, acetoacetate, beta-hydroxybutyrate) or shunted into the TCA cycle to generate energy for gluconeogenesis. During starvation, most tissues utilize a combination of FFAs and ketones for their energy needs. Important exceptions include the brain (FFAs do not cross the blood-brain barrier, so only ketone bodies/glucose can be used) and erythrocytes (can use only glucose due to lack of mitochondria).

(Choice A) Glycogen phosphorylase is the rate-limiting enzyme in glycogenolysis, a process that frees glucose-1-phosphate from stored glycogen chains. Glycogenolysis increases blood glucose levels during the first several hours of fasting but has no effect on fatty acid oxidation.

(Choice C) Lipoprotein lipase is an enzyme found on endothelial cells that functions to degrade triglycerides found in chylomicrons and VLDL. Although it is functionally similar to HSL, it works in the bloodstream to form FFAs that are then transported into adipocytes storage or used by tissues (eg, heart/skeletal muscle) for energy production.

(Choice D) Mitochondrial HMG-CoA synthase plays a role in the production of ketones. Although it could be responsible for the presence of urinary ketone bodies in this patient, it would not account for the maintenance of blood glucose levels.

(Choice E) Phosphofructokinase-1 catalyzes the major rate-limiting step in glycolysis by converting fructose-6-phosphate to fructose-1,6-bisphosphate. It is not involved in gluconeogenesis or ketone production.

Educational objective:
Hormone-sensitive lipase is found in adipose tissue, where it functions to drive the breakdown of stored

https://t.me/USMLEWorldStep1

triglycerides into **free fatty acids** (FFAs) and **glycerol**. HSL is activated in response to stress hormones (eg, catecholamines, glucagon, ACTH), whereas it is inhibited by the release of insulin. The stress hormones stimulate Gs protein-coupled receptors on adipocytes, leading to increased cAMP production and activation of protein kinase A (PKA). Finally, PKA phosphorylates and activates HSL, stimulating lipolysis.

FFAs and glycerol released into the circulation can be taken up by the liver, where the glycerol is used primarily as a carbon source for **gluconeogenesis**. The liver oxidizes the FFAs to acetyl-coA, which can then be further metabolized to **ketone bodies** (eg, acetoacetate, beta-hydroxybutyrate) or shunted into the TCA cycle to generate energy for gluconeogenesis. During starvation, most tissues utilize a combination of FFAs and ketones for their energy needs. Important exceptions include the brain (FFAs do not cross the blood-brain barrier, so only ketone bodies/glucose can be used) and erythrocytes (can use only glucose due to lack of mitochondria).

(Choice A) Glycogen phosphorylase is the rate-limiting enzyme in glycogenolysis, a process that frees glucose-1-phosphate from stored glycogen chains. Glycogenolysis increases blood glucose levels during the first several hours of fasting but has no effect on fatty acid oxidation.

(Choice C) Lipoprotein lipase is an enzyme found on endothelial cells that functions to degrade triglycerides found in chylomicrons and VLDL. Although it is functionally similar to HSL, it works in the bloodstream to form FFAs that are then transported into adipocytes storage or used by tissues (eg, heart/skeletal muscle) for energy production.

(Choice D) Mitochondrial HMG-CoA synthase plays a role in the production of ketones. Although it could be responsible for the presence of urinary ketone bodies in this patient, it would not account for the maintenance of blood glucose levels.

(Choice E) Phosphofructokinase-1 catalyzes the major rate-limiting step in glycolysis by converting fructose-6-phosphate to fructose-1,6-bisphosphate. It is not involved in gluconeogenesis or ketone production.

Educational objective:
Hormone-sensitive lipase is found in adipose tissue, where it functions to drive the breakdown of stored triglycerides into free fatty acids and glycerol. During times of starvation, this enzyme provides substrates for hepatic gluconeogenesis and ketone body formation.

References

https://t.me/USMLEWorldStep1

A (PKA). Finally, PKA phosphorylates and activates HSL, stimulating lipolysis.

FFAs and glycerol released into the circulation can be taken up by the liver, where the glycerol is used primarily as a carb
metab
energy
energy
bodies

(Choi
phosp
hours

(Choi
in chyl
are the

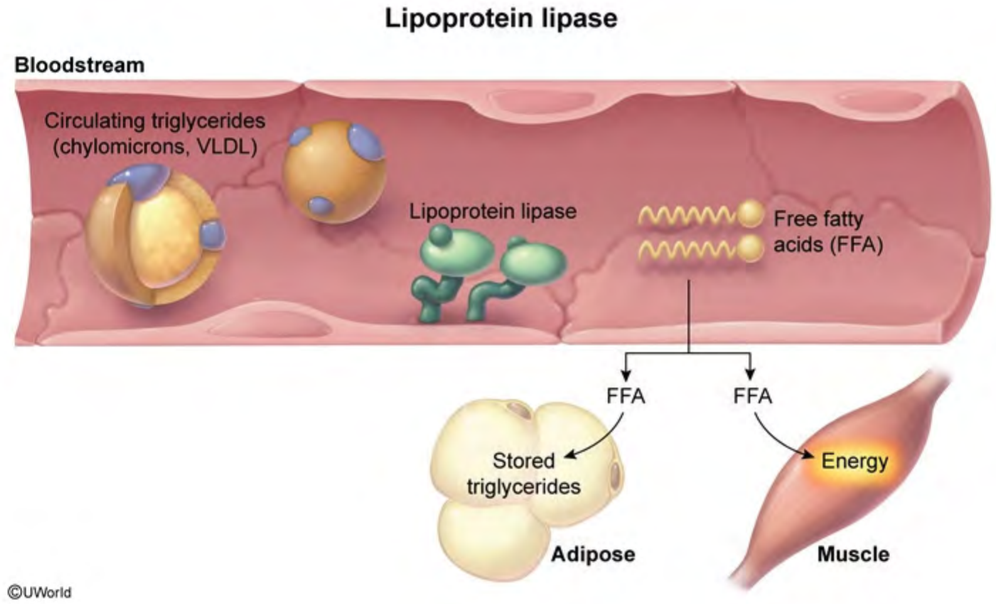
(Choi
respor
blood

(Choi
phosp

Educa
Hormo
triglyce
hepati

Refere
- Lip

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Biochemistry (Subject) | Endocrine, Diabetes & Metabolism (System) | Triglyceride metabolism (Topic)

https://t.me/USMLEWorldStep1

A 55-year-old man comes to the office to establish care after relocating to the area. The patient has a 6-year history of type 2 diabetes mellitus for which he takes metformin monotherapy. He feels well and has no other medical conditions. The patient does not use tobacco or alcohol. He consumes a balanced diet and jogs for 40 minutes every morning. Review of his blood glucose journal over the last few months shows fasting glucose levels of 150-180 mg/dL. Laboratory analysis shows a hemoglobin A1c level of 4%. Further evaluation with hemoglobin electrophoresis shows a hemoglobin A2 level of 7.5% (normal: 1.5%-3.5%). Which of the following is the most likely explanation for this patient's lower-than-expected hemoglobin A1c level?

- A. Beta-thalassemia minor
- B. Folate deficiency
- C. Iron deficiency
- D. Low erythropoietin
- E. Poor glycemic control
- F. Sickle cell trait

Submit

https://t.me/USMLEWorldStep1

A 55-year-old man comes to the office to establish care after relocating to the area. The patient has a 6-year history of type 2 diabetes mellitus for which he takes metformin monotherapy. He feels well and has no other medical conditions. The patient does not use tobacco or alcohol. He consumes a balanced diet and jogs for 40 minutes every morning. Review of his blood glucose journal over the last few months shows fasting glucose levels of 150-180 mg/dL. Laboratory analysis shows a hemoglobin A1c level of 4%. Further evaluation with hemoglobin electrophoresis shows a hemoglobin A2 level of 7.5% (normal: 1.5%-3.5%). Which of the following is the most likely explanation for this patient's lower-than-expected hemoglobin A1c level?

- ✓ A. Beta-thalassemia minor (76%)
- B. Folate deficiency (1%)
- ✗ C. Iron deficiency (2%)
- D. Low erythropoietin (4%)
- E. Poor glycemic control (1%)
- F. Sickle cell trait (12%)

Incorrect
Correct answer
A

76%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

Hemoglobin A1c is produced by irreversible nonenzymatic glycosylation of the N-terminal of the hemoglobin molecule. The degree of glycosylation (ie, hemoglobin A1c level) directly correlates with average blood glucose levels over the life span of circulating erythrocytes, which is normally approximately 3 months. **Higher glucose levels** and **increased exposure time** of red cells to glucose **increase hemoglobin A1c** values. As such, conditions that alter red blood cell survival time also affect hemoglobin A1c levels.

This patient has an elevated hemoglobin A2, which suggests comorbid **beta-thalassemia minor**. Hemoglobin A2

https://t.me/USMLEWorldStep1

Hemoglobin A1c is produced by irreversible nonenzymatic glycosylation of the N-terminal of the hemoglobin molecule. The degree of glycosylation (ie, hemoglobin A1c level) directly correlates with average blood glucose levels over the life span of circulating erythrocytes, which is normally approximately 3 months. **Higher glucose levels** and **increased exposure time** of red cells to glucose **increase hemoglobin A1c** values. As such, conditions that alter red blood cell survival time also affect hemoglobin A1c levels.

This patient has an elevated hemoglobin A2, which suggests comorbid **beta-thalassemia minor**. Hemoglobin A2 is elevated in beta-thalassemia to compensate for beta-globin–chain underproduction, but results in microcytic red cells that are prone to hemolysis. **Increased erythrocyte turnover** results in a **misleadingly low hemoglobin A1c level**. In such cases, measurement of glycated serum proteins (ie, fructosamine) is sometimes used to estimate glycemic control.

(Choices B and C) Deficiencies of iron, folate, and vitamin B_{12} can reduce production of new red cells, leading to a preponderance of older erythrocytes and falsely elevated hemoglobin A1c. In contrast, treatment of vitamin deficiencies causes young red cells to be rapidly released into circulation, falsely lowering hemoglobin A1c.

(Choice D) Advanced diabetic nephropathy may cause reduced erythropoietin production. The resulting decrease in production of new red cells may lead to falsely high hemoglobin A1c (similar to nutrient deficiencies).

(Choice E) Chronically elevated blood glucose (ie, poor glycemic control) is the primary cause of increased hemoglobin A1c in patients with diabetes.

(Choice F) Sickle cell trait is characterized by heterozygous carriage of hemoglobin S. Some patients with sickle cell trait can have slightly reduced hemoglobin A1c level due to increased red cell turnover (homozygous individuals with sickle cell disease have rapid red cell turnover and very low A1c). However, hemoglobin A2 percentage remains near normal in patients with sickle cell mutations.

Educational objective:
Hemoglobin A1c is produced by nonenzymatic glycosylation of the hemoglobin molecule. A hemoglobin A1c assay provides an estimate of chronic glycemic control over the life span of circulating erythrocytes (~3 months). However, rapid erythrocyte turnover (eg, hemolytic anemia) can give a misleadingly low hemoglobin A1c in relation to glycemic status.

https://t.me/USMLEWorldStep1

Hemoglobin A1c is produced by irreversible nonenzymatic glycosylation of the N-terminal of the hemoglobin molec
levels
levels
conditi

This p
is elev
cells th
A1c le
estima

(Choi
a prep
deficie

(Choi
in proc

(Choi
hemog

(Choi
cell tra
individ
percer

Educa
Hemo
provid
Howe
to glycemic status.

Exhibit Display

Hemoglobin electrophoresis patterns in sickle cell & beta-thalassemia

Condition	Hemoglobin A	Hemoglobin A2	Hemoglobin F	Hemoglobin S
Normal	95%-98%	~2.5%	<1%	Absent
Beta-thalassemia minor	↓	↑	Near normal	Absent
Beta-thalassemia major	Absent	↑↑	↑↑	Absent
Sickle cell trait	↓↓	Near normal	Near normal	↑
Sickle cell disease	Absent	Near normal	↑↑	↑↑

New | Existing | My Notebook

https://t.me/USMLEWorldStep1

A 20-year-old woman is brought to the emergency department due to intractable vomiting and abdominal pain. She has a several-week history of anorexia and weight loss. The patient has well-controlled primary hypothyroidism treated with levothyroxine but has not taken her medication for 2 days because of vomiting. Temperature is 37.6 C (99.7 F), blood pressure is 80/40 mm Hg, pulse is 120/min, and respirations are 18/min. On physical examination, she is mildly lethargic but oriented. Generalized hyperpigmentation is present and is most conspicuous over the face, neck, and dorsal surface of the hands. Urinalysis and chest x-ray are within normal limits. Finger-stick blood glucose is 60 mg/dL. A 1-L bolus of normal saline is rapidly infused, and high-flow intravenous fluids are continued. This patient also requires immediate treatment with which of the following medications?

- A. Ceftriaxone
- B. Dexamethasone
- C. Dopamine
- D. Epinephrine
- E. Levothyroxine

Submit

https://t.me/USMLEWorldStep1

A 20-year-old woman is brought to the emergency department due to intractable vomiting and abdominal pain. She has a several-week history of anorexia and weight loss. The patient has well-controlled primary hypothyroidism treated with levothyroxine but has not taken her medication for 2 days because of vomiting. Temperature is 37.6 C (99.7 F), blood pressure is 80/40 mm Hg, pulse is 120/min, and respirations are 18/min. On physical examination, she is mildly lethargic but oriented. Generalized hyperpigmentation is present and is most conspicuous over the face, neck, and dorsal surface of the hands. Urinalysis and chest x-ray are within normal limits. Finger-stick blood glucose is 60 mg/dL. A 1-L bolus of normal saline is rapidly infused, and high-flow intravenous fluids are continued. This patient also requires immediate treatment with which of the following medications?

- ✗ A. Ceftriaxone (3%)
- ✓ B. Dexamethasone (56%)
- C. Dopamine (4%)
- D. Epinephrine (18%)
- E. Levothyroxine (15%)

Incorrect
Correct answer
B

56%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

Acute adrenal insufficiency (adrenal crisis)	
Etiology	• Adrenal hemorrhage or infarction • Illness/injury/surgery in patient with chronic AI • Pituitary apoplexy

https://t.me/USMLEWorldStep1

Acute adrenal insufficiency (adrenal crisis)	
Etiology	• Adrenal hemorrhage or infarction • Illness/injury/surgery in patient with chronic AI • Pituitary apoplexy
Clinical features	• **Hypotension** & **shock** • Nausea, vomiting, abdominal pain • Fever, generalized weakness
Treatment	• **Hydrocortisone** or **dexamethasone** • Rapid intravenous volume repletion
AI = adrenal insufficiency.	

This patient most likely has acute **adrenal crisis**. Her history of hypothyroidism puts her at increased risk for other autoimmune endocrinopathies (eg, autoimmune adrenalitis), and her weight loss and hyperpigmentation are suggestive of chronic **primary adrenal insufficiency** (Addison disease). In normal individuals, the adrenal glands respond to acute stress (eg, illness, surgery) with a compensatory increase in glucocorticoid production, but patients with adrenal insufficiency cannot mount such a response.

Adrenal crisis is characterized by **severe hypotension** and refractory shock. Associated symptoms include abdominal pain, vomiting, weakness, and fever. In addition to aggressive **fluid resuscitation**, treatment of adrenal crisis requires immediate **glucocorticoid supplementation** with hydrocortisone or dexamethasone. Treatment should begin immediately without waiting for results of diagnostic studies, and the response is usually rapid.

(Choice A) Antibiotics may be necessary if evidence of infection is found. However, treatment with glucocorticoids is warranted immediately, whereas the decision to start an antibiotic may be made when the presence of infection is more clearly established.

(Choices C and D) Dopamine is used in the treatment of shock and refractory cardiac failure. Epinephrine is used in the treatment of anaphylaxis, severe asthma, and cardiac arrest. However, hypotension in adrenal crisis is often refractory to vasopressors because glucocorticoids have a permissive effect on vasoconstriction.

https://t.me/USMLEWorldStep1

	Rapid intravenous volume replacement

AI = adrenal insufficiency.

This patient most likely has acute **adrenal crisis**. Her history of hypothyroidism puts her at increased risk for other autoimmune endocrinopathies (eg, autoimmune adrenalitis), and her weight loss and hyperpigmentation are suggestive of chronic **primary adrenal insufficiency** (Addison disease). In normal individuals, the adrenal glands respond to acute stress (eg, illness, surgery) with a compensatory increase in glucocorticoid production, but patients with adrenal insufficiency cannot mount such a response.

Adrenal crisis is characterized by **severe hypotension** and refractory shock. Associated symptoms include abdominal pain, vomiting, weakness, and fever. In addition to aggressive **fluid resuscitation**, treatment of adrenal crisis requires immediate **glucocorticoid supplementation** with hydrocortisone or dexamethasone. Treatment should begin immediately without waiting for results of diagnostic studies, and the response is usually rapid.

(Choice A) Antibiotics may be necessary if evidence of infection is found. However, treatment with glucocorticoids is warranted immediately, whereas the decision to start an antibiotic may be made when the presence of infection is more clearly established.

(Choices C and D) Dopamine is used in the treatment of shock and refractory cardiac failure. Epinephrine is used in the treatment of anaphylaxis, severe asthma, and cardiac arrest. However, hypotension in adrenal crisis is often refractory to vasopressors because glucocorticoids have a permissive effect on vasoconstriction.

(Choice E) Clinical features of hypothyroid crisis may include hypoglycemia and hypotension, as seen in this patient, but would usually also include altered sensorium, hypothermia, bradycardia, and hypoventilation. In addition, due to the long plasma half life of levothyroxine, missing 2 days of therapy would be unlikely to cause a symptomatic drop in thyroid hormone levels.

Educational objective:
Patients with adrenal insufficiency are not able to increase glucocorticoid production in response to acute stress (eg, illness, surgery). Adrenal crisis is characterized by severe hypotension, abdominal pain, vomiting, weakness, and fever. In addition to aggressive fluid resuscitation, treatment requires immediate glucocorticoid supplementation.

References

https://t.me/USMLEWorldStep1

A 48-year-old woman with a complex medical history comes to the clinic due to a change in her body habitus. She says her legs are "like sticks" while her "belly is getting bigger." The patient also feels increasingly fatigued but does not have excessive daytime somnolence. She has been homeless for much of the last 5 years but has been living in a residential care facility for the last 12 months. On physical examination, she is distractible and has an inappropriate affect but is cooperative. Neurologic and mental status examination is otherwise normal. There is loss of adipose tissue from the extremities and face, with a noticeable increase in abdominal girth. Which of the following types of medications is most likely to be responsible for this patient's symptoms?

- A. Antiretroviral medication
- B. HMG-CoA reductase inhibitor
- C. Loop diuretic
- D. Nonsteroidal antiinflammatory drug
- E. Proton pump inhibitor
- F. Selective serotonin reuptake inhibitor
- G. Thyroperoxidase inhibitor

Submit

https://t.me/USMLEWorldStep1

A 48-year-old woman with a complex medical history comes to the clinic due to a change in her body habitus. She says her legs are "like sticks" while her "belly is getting bigger." The patient also feels increasingly fatigued but does not have excessive daytime somnolence. She has been homeless for much of the last 5 years but has been living in a residential care facility for the last 12 months. On physical examination, she is distractible and has an inappropriate affect but is cooperative. Neurologic and mental status examination is otherwise normal. There is loss of adipose tissue from the extremities and face, with a noticeable increase in abdominal girth. Which of the following types of medications is most likely to be responsible for this patient's symptoms?

- ✓ A. Antiretroviral medication (53%)
- ✗ B. HMG-CoA reductase inhibitor (7%)
- C. Loop diuretic (2%)
- D. Nonsteroidal antiinflammatory drug (3%)
- E. Proton pump inhibitor (1%)
- F. Selective serotonin reuptake inhibitor (11%)
- G. Thyroperoxidase inhibitor (20%)

Incorrect
Correct answer
A

53%
Answered correctly

04 secs
Time Spent

2023
Version

Explanation

This patient has **redistribution of fat** from the extremities to the trunk. Medication-induced body fat redistribution (sometimes called **lipoatrophy** or **lipodystrophy**) is a common adverse effect of **highly-active antiretroviral therapy (HAART)** and can be considered a product of 2 independent processes: wasting of fat from the face and extremities and deposition of fat in the trunk and viscera.

1. **Lipoatrophy** refers to loss of subcutaneous fat, especially from the face, extremities, and buttocks. It is

https://t.me/USMLEWorldStep1

This patient has **redistribution of fat** from the extremities to the trunk. Medication-induced body fat redistribution (sometimes called **lipoatrophy** or **lipodystrophy**) is a common adverse effect of **highly-active antiretroviral therapy (HAART)** and can be considered a product of 2 independent processes: wasting of fat from the face and extremities and deposition of fat in the trunk and viscera.

1. **Lipoatrophy** refers to loss of subcutaneous fat, especially from the face, extremities, and buttocks. It is primarily seen in patients taking nucleoside reverse transcriptase inhibitors (mainly stavudine and zidovudine) and is also associated with protease inhibitor use.
2. **Central fat deposition** also occurs in some patients and causes increased abdominal girth and a buffalo hump (dorsocervical fat accumulation) that is similar to Cushing syndrome. Central fat deposition may be seen with any HIV treatment regimen and may be a result of treating HIV rather than a specific medication adverse effect.

Both syndromes have been associated with **metabolic abnormalities** including insulin resistance, hypertriglyceridemia, and reduced HDL cholesterol levels.

(Choice B) HMG-CoA reductase inhibitors (statins) are associated with myalgias and an increase in hepatic transaminase levels. They do not cause fat redistribution.

(Choice C) Thiazide diuretics (eg, chlorthalidone, hydrochlorothiazide) can cause hyperglycemia and hypertriglyceridemia and may have a small effect on fat distribution. However, these effects have not been seen with loop diuretics (eg, furosemide).

(Choice D) Unlike glucocorticoids, nonsteroidal antiinflammatory drugs (NSAIDs) do not significantly alter tissue lipid metabolism or cause fat redistribution.

(Choice E) Proton pump inhibitors (PPIs) are used to reduce gastric acid secretion in patients with peptic ulcer and gastroesophageal reflux. PPIs can cause hypomagnesemia and increased risk of osteoporosis.

(Choice F) Selective serotonin reuptake inhibitors are indicated for treatment of depression and chronic anxiety. They can cause weight gain in a subset of patients but have not been linked to fat redistribution.

(Choice G) Thyroperoxidase inhibitors (eg, methimazole, propylthiouracil) are used to treat hyperthyroidism.

https://t.me/USMLEWorldStep1

and is also associated with protease inhibitor use.

2. **Central fat deposition** also occurs in some patients and causes increased abdominal girth and a buffalo hump (dorsocervical fat accumulation) that is similar to Cushing syndrome. Central fat deposition may be seen with any HIV treatment regimen and may be a result of treating HIV rather than a specific medication adverse effect.

Both syndromes have been associated with **metabolic abnormalities** including insulin resistance, hypertriglyceridemia, and reduced HDL cholesterol levels.

(Choice B) HMG-CoA reductase inhibitors (statins) are associated with myalgias and an increase in hepatic transaminase levels. They do not cause fat redistribution.

(Choice C) Thiazide diuretics (eg, chlorthalidone, hydrochlorothiazide) can cause hyperglycemia and hypertriglyceridemia and may have a small effect on fat distribution. However, these effects have not been seen with loop diuretics (eg, furosemide).

(Choice D) Unlike glucocorticoids, nonsteroidal antiinflammatory drugs (NSAIDs) do not significantly alter tissue lipid metabolism or cause fat redistribution.

(Choice E) Proton pump inhibitors (PPIs) are used to reduce gastric acid secretion in patients with peptic ulcer and gastroesophageal reflux. PPIs can cause hypomagnesemia and increased risk of osteoporosis.

(Choice F) Selective serotonin reuptake inhibitors are indicated for treatment of depression and chronic anxiety. They can cause weight gain in a subset of patients but have not been linked to fat redistribution.

(Choice G) Thyroperoxidase inhibitors (eg, methimazole, propylthiouracil) are used to treat hyperthyroidism. Common side effects include bone marrow suppression (eg, anemia, agranulocytosis).

Educational objective:
Highly-active antiretroviral therapy (HAART) for HIV is commonly associated with body fat redistribution. Subcutaneous lipoatrophy involving the face and extremities is associated with nucleoside reverse transcriptase inhibitors (especially stavudine and zidovudine) and protease inhibitors. Central fat accumulation in the trunk and viscera can occur with any HAART regimen.

https://t.me/USMLEWorldStep1

G. Thyroperoxidase inhibitor (20%)

Inco
Corre
A

Expl

This p
(some
therap
extrem

1. **L**
   p
   a
2. **C**
   h
   s
   a

Both s
hypert

(Choi
transa

(Choi
hypert
with lo

(Choice D) Unlike glucocorticoids, nonsteroidal antiinflammatory drugs (NSAIDs) do not significantly alter tissue

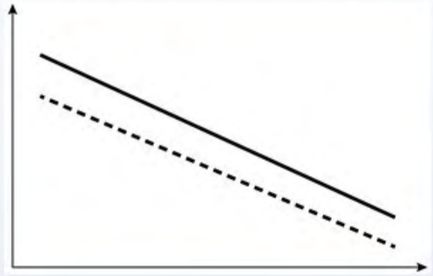
Exhibit Display

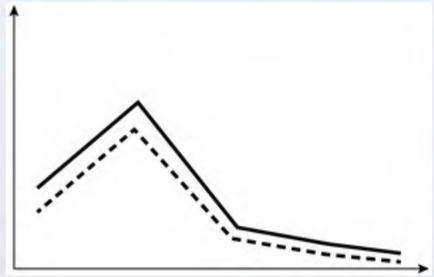


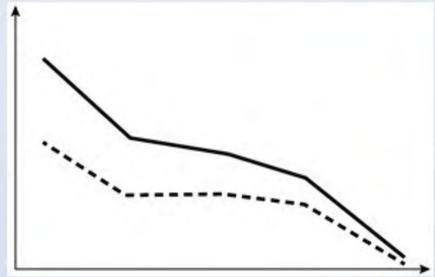
Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

A 60-year-old man comes to the office due to 2 months of low back pain unresponsive to over-the-counter analgesics. The pain is worse at night and interferes with sleep. On examination, the lumbar vertebrae are tender to palpation, and the prostate is indurated and firm. After a thorough evaluation, leuprolide therapy is started. Which of the following changes in testosterone (solid line) and dihydrotestosterone (dashed line) levels are most likely to occur in this patient after initiation of therapy?

A.


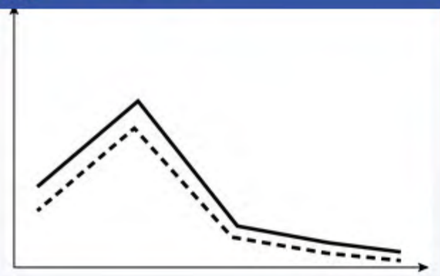
B.


C.


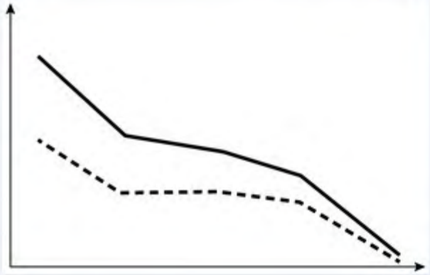
D.


https://t.me/USMLEWorldStep1

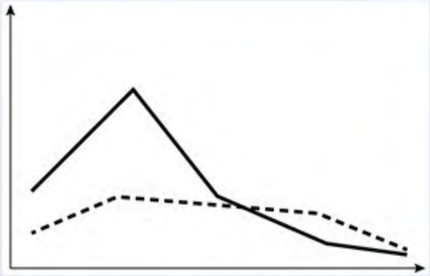
B.



C.



D.



E.

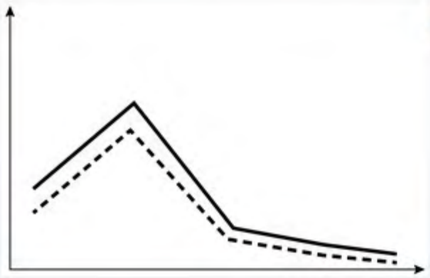


Submit

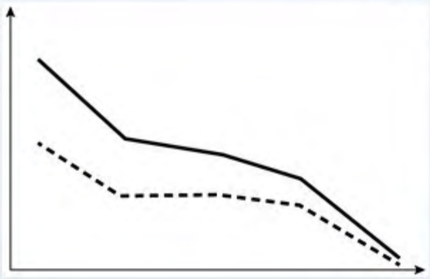
https://t.me/USMLEWorldStep1



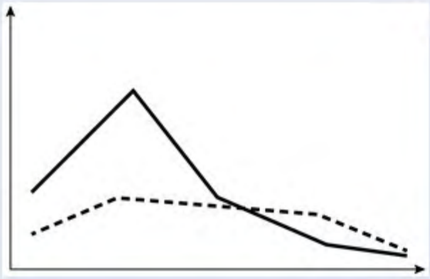
✓ ○ B. (59%)



○ C. (8%)



✗ ◉ D. (17%)



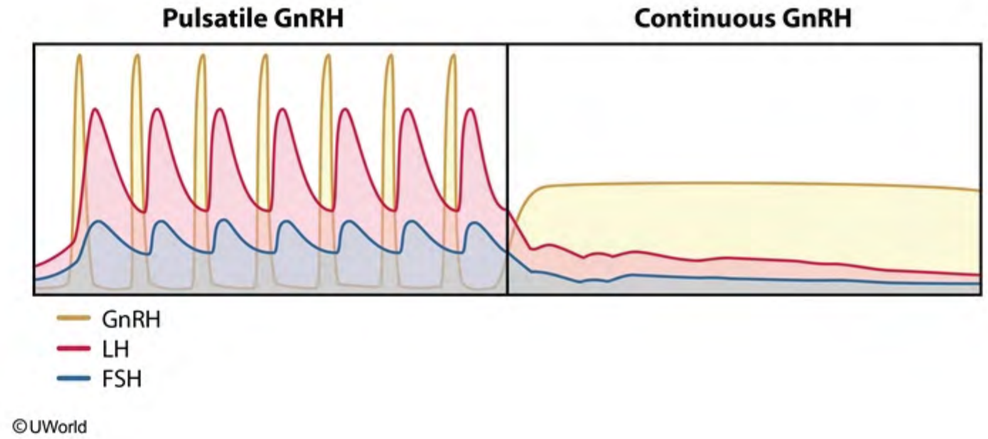
○ E. (2%)



https://t.me/USMLEWorldStep1

E. (2%)

Exhibit Display



Zoom In Zoom Out Reset New | Existing My Notebook

androgen production via surgical or medical **orchiectomy**.

https://t.me/USMLEWorldStep1

This patient's nocturnal back pain, spinal tenderness, and indurated prostate suggest **prostate adenocarcinoma** with bony metastases. Prostate cancer is an **androgen-dependent** tumor. Because most androgens (eg, testosterone) in men are made in the Leydig cells of the testes, initial treatment focuses on a systemic reduction in androgen production via surgical or medical **orchiectomy**.

Androgen production is primarily regulated by the hypothalamic-pituitary-testicular axis. Neurons in the hypothalamus release **GnRH** into the hypothalamic-pituitary portal system in a **pulsatile pattern** every 90-120 minutes. This stimulates pituitary gonadotrophs to release luteinizing hormone (**LH**) into the circulation, which then binds to a surface receptor on Leydig cells and stimulates androgen production.

In medical orchiectomy, a **GnRH analogue** (eg, **leuprolide**) is administered to continuously stimulate pituitary gonadotrophs, which leads to down-regulation of the GnRH receptor, lower LH release, and reduced testicular androgen production. However, because GnRH analogues **initially stimulate** pituitary gonadotrophs prior to the down-regulation of the receptor, most patients have a **transient increase in systemic androgens** during the first week of therapy (upward portion of graph). This effect is generally blunted by administering a short course of androgen receptor antagonist medication (eg, bicalutamide) during treatment initiation in order to prevent worsening of the underlying prostate cancer.

(Choices A and C) GnRH analogues stimulate the GnRH receptor prior to down-regulation, resulting in a transient increase in LH and systemic androgen production prior to down-regulation of the receptor.

(Choice D) The enzyme 5-alpha reductase converts testosterone to dihydrotestosterone (DHT) in peripheral tissues (eg, skin, liver); as testosterone levels fall, DHT production will decrease concurrently. GnRH analogues have no effect on the activity of 5-alpha reductase, therefore, testosterone and DHT levels rise and fall in synchrony following GnRH administration.

(Choice E) Benign prostatic hyperplasia is typically treated with a 5-alpha reductase inhibitor (eg, finasteride), which reduces the conversion of testosterone to DHT. This class of medications reduces DHT levels while testosterone levels remain largely unaffected.

Educational objective:
Leuprolide is a GnRH agonist used to treat prostate cancer. It initially stimulates pituitary LH secretion, which leads to a rise in androgen levels. However, the GnRH receptor is subsequently down-regulated, which

https://t.me/USMLEWorldStep1

androgen production via surgical or medical **orchiectomy**.

Androgen production is primarily regulated by the hypothalamic-pituitary-testicular axis. Neurons in the hypothalamus release **GnRH** into the hypothalamic-pituitary portal system in a **pulsatile pattern** every 90-120 minutes. This stimulates pituitary gonadotrophs to release luteinizing hormone (**LH**) into the circulation, which then binds to a surface receptor on Leydig cells and stimulates androgen production.

In medical orchiectomy, a **GnRH analogue** (eg, **leuprolide**) is administered to continuously stimulate pituitary gonadotrophs, which leads to down-regulation of the GnRH receptor, lower LH release, and reduced testicular androgen production. However, because GnRH analogues **initially stimulate** pituitary gonadotrophs prior to the down-regulation of the receptor, most patients have a **transient increase in systemic androgens** during the first week of therapy (upward portion of graph). This effect is generally blunted by administering a short course of androgen receptor antagonist medication (eg, bicalutamide) during treatment initiation in order to prevent worsening of the underlying prostate cancer.

(Choices A and C) GnRH analogues stimulate the GnRH receptor prior to down-regulation, resulting in a transient increase in LH and systemic androgen production prior to down-regulation of the receptor.

(Choice D) The enzyme 5-alpha reductase converts testosterone to dihydrotestosterone (DHT) in peripheral tissues (eg, skin, liver); as testosterone levels fall, DHT production will decrease concurrently. GnRH analogues have no effect on the activity of 5-alpha reductase, therefore, testosterone and DHT levels rise and fall in synchrony following GnRH administration.

(Choice E) Benign prostatic hyperplasia is typically treated with a 5-alpha reductase inhibitor (eg, finasteride), which reduces the conversion of testosterone to DHT. This class of medications reduces DHT levels while testosterone levels remain largely unaffected.

Educational objective:
Leuprolide is a GnRH agonist used to treat prostate cancer. It initially stimulates pituitary LH secretion, which leads to a rise in androgen levels. However, the GnRH receptor is subsequently down-regulated, which dramatically drops LH release and leads to a long-term decrease in androgen production.

References

- Impact of surgical and medical castration on serum testosterone level in prostate cancer patients.

https://t.me/USMLEWorldStep1

A 24-year-old woman is admitted to the hospital with a diagnosis of acute appendicitis. She started having right lower quadrant abdominal pain approximately 30 hours earlier but did not go to the hospital because she thought the pain would subside on its own. The patient had no food, only sips of water, during that time. Blood pressure is 115/72 mm Hg and pulse is 106/min. Mucous membranes are dry and there is tenderness in the right lower quadrant of the abdomen. Laboratory evaluation shows mild leukocytosis, normal serum electrolytes, borderline low serum glucose levels, and moderate ketones in the urine. Based on the evaluation, it is suspected that this patient is utilizing ketone bodies as a significant reserve of energy. Which of the following tissues cannot use this energy source?

- A. Brain
- B. Erythrocytes
- C. Heart muscle
- D. Renal cortex
- E. Skeletal muscle

Submit

https://t.me/USMLEWorldStep1

A 24-year-old woman is admitted to the hospital with a diagnosis of acute appendicitis. She started having right lower quadrant abdominal pain approximately 30 hours earlier but did not go to the hospital because she thought the pain would subside on its own. The patient had no food, only sips of water, during that time. Blood pressure is 115/72 mm Hg and pulse is 106/min. Mucous membranes are dry and there is tenderness in the right lower quadrant of the abdomen. Laboratory evaluation shows mild leukocytosis, normal serum electrolytes, borderline low serum glucose levels, and moderate ketones in the urine. Based on the evaluation, it is suspected that this patient is utilizing ketone bodies as a significant reserve of energy. Which of the following tissues cannot use this energy source?

- ✗ A. Brain (13%)
- ✓ B. Erythrocytes (79%)
- C. Heart muscle (1%)
- D. Renal cortex (1%)
- E. Skeletal muscle (4%)

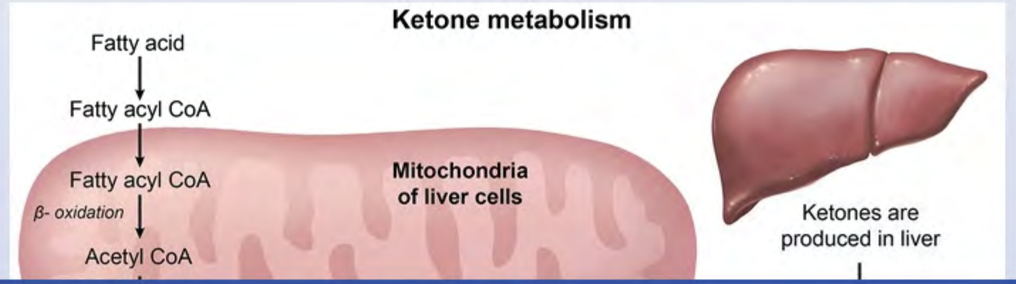
Incorrect
Correct answer
B

79%
Answered correctly

03 secs
Time Spent

2023
Version

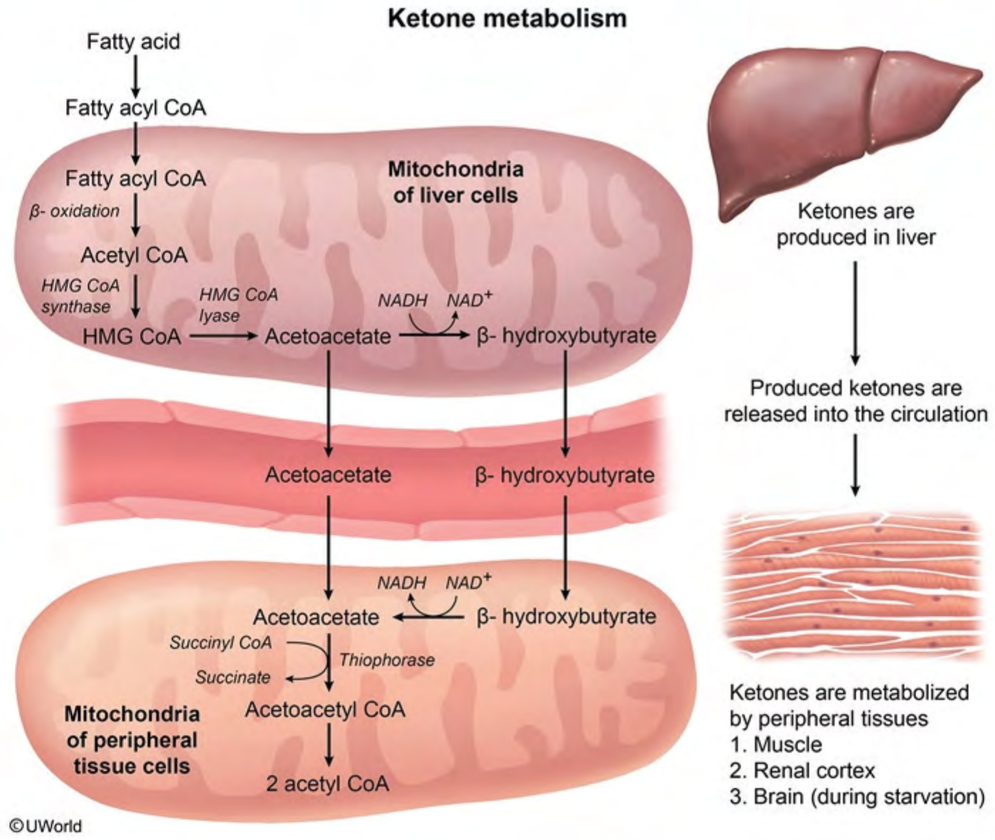
Explanation



https://t.me/USMLEWorldStep1

A 24-year-old woman is admitted to the hospital with a diagnosis of acute appendicitis. She started having right lower
the pa
115/72
quadra
low se
patien
energy

Exhibit Display



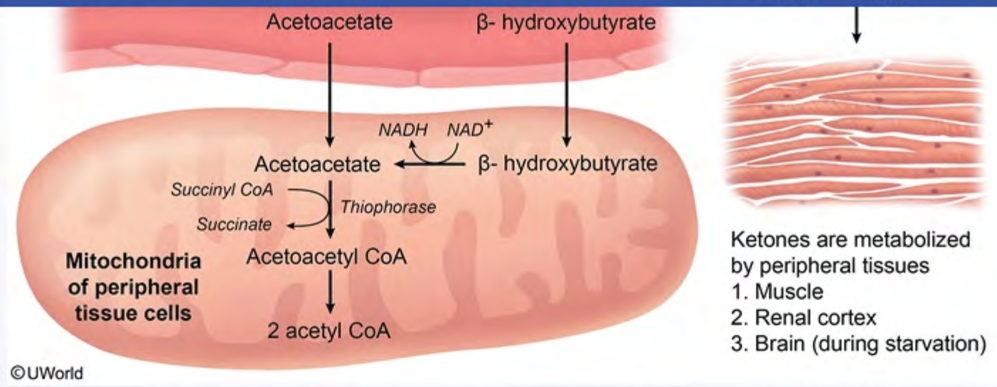
Ketones are produced in liver

Produced ketones are released into the circulation

Ketones are metabolized by peripheral tissues
1. Muscle
2. Renal cortex
3. Brain (during starvation)

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1



Ketones are metabolized by peripheral tissues
1. Muscle
2. Renal cortex
3. Brain (during starvation)

After about 12-18 hours of **fasting**, the body's glycogen stores are depleted and **gluconeogenesis** is required to maintain blood glucose levels. As fasting continues, the body limits its reliance on gluconeogenesis in an effort to conserve protein and resorts instead to **ketone body synthesis**. Ketone bodies are generated in the liver from fatty acids and yield energy when converted to acetyl CoA in the **mitochondria** of target cells.

The brain, kidneys, cardiac muscle, and skeletal muscle **(Choices A, C, D & E)** can all utilize ketones for energy. In the initial stages of fasting, the heart and skeletal muscle consume primarily ketone bodies to preserve glucose for the brain, but in prolonged starvation, even the brain will utilize ketone bodies for the majority of its energy needs. However, erythrocytes cannot use ketone bodies for energy because they lack mitochondria. The liver is also unable to utilize ketone bodies for energy because it lacks the enzyme succinyl CoA-acetoacetate CoA transferase (thiophorase), which is required to convert acetoacetate to acetoacetyl CoA.

Educational objective:
When glycogen stores are depleted during fasting, ketone bodies are produced in the liver and can be used as an energy source in the mitochondria of peripheral tissues. The brain preferentially uses glucose, but will utilize ketones for most of its energy needs during prolonged starvation. Erythrocytes lack mitochondria and are unable to use ketones.

Biochemistry	Endocrine, Diabetes & Metabolism	Gluconeogenesis
Subject	System	Topic

Copyright © UWorld. All rights reserved.

https://t.me/USMLEWorldStep1

A 16-year-old girl comes to the office for a pre-participatory school sports examination. She plays on her high school soccer team and also frequently competes in local beauty pageants. The patient follows strict dietary limitations and exercises strenuously 2 hours a day. Onset of menses was at age 13, but her last menstrual period was 8 months ago. She otherwise feels well. Her height is 165 cm (5 ft 5 in) and her weight is 45.3 kg (100 lb), with a BMI of 16.6 kg/m^2. Physical examination shows a pale and thin girl with fine hair around her trunk, but the remainder is otherwise normal. Urine pregnancy test is negative. Which of the following is the most likely mechanism of her amenorrhea?

- A. Hyperprolactinemia
- B. Hyperthyroidism
- C. Hypothalamic suppression
- D. Primary ovarian failure
- E. Primary pituitary dysfunction

Submit

https://t.me/USMLEWorldStep1

A 16-year-old girl comes to the office for a pre-participatory school sports examination. She plays on her high school soccer team and also frequently competes in local beauty pageants. The patient follows strict dietary limitations and exercises strenuously 2 hours a day. Onset of menses was at age 13, but her last menstrual period was 8 months ago. She otherwise feels well. Her height is 165 cm (5 ft 5 in) and her weight is 45.3 kg (100 lb), with a BMI of 16.6 kg/m^2. Physical examination shows a pale and thin girl with fine hair around her trunk, but the remainder is otherwise normal. Urine pregnancy test is negative. Which of the following is the most likely mechanism of her amenorrhea?

- A. Hyperprolactinemia (3%)
- ✗ B. Hyperthyroidism (3%)
- ✓ C. Hypothalamic suppression (80%)
- D. Primary ovarian failure (7%)
- E. Primary pituitary dysfunction (6%)

Incorrect
Correct answer
C

80%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

Functional hypothalamic amenorrhea

Excessive weight loss
Strenuous exercise
Chronic illness
Eating disorder

↓

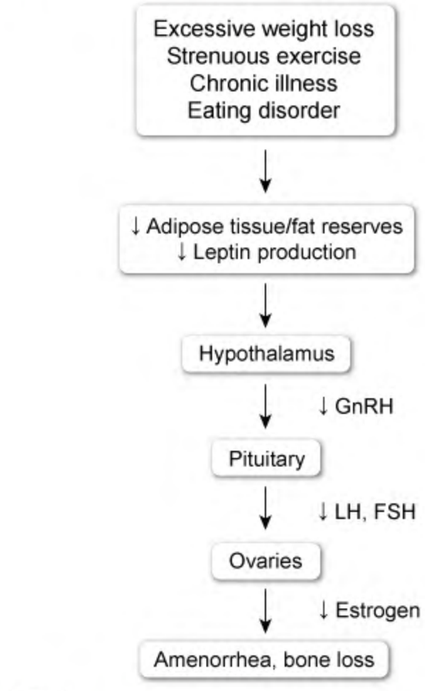
↓ Adipose tissue/fat reserves

https://t.me/USMLEWorldStep1

A 16-year-old girl comes to the office for a pre-participatory school sports examination. She plays on her high
school
limitati
was 8
with a
remair
mecha

Exhibit Display

Functional hypothalamic amenorrhea



©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Inco
Corre
C

Expl

↓ Adipose tissue/fat reserves

https://t.me/USMLEWorldStep1

Amenorrhea can be categorized as primary (failure of menarche prior to age 15) or secondary (cessation of menstruation in premenopausal women who previously have had menses). Secondary amenorrhea can be due to hypothalamic, pituitary, ovarian, uterine, or other endocrine (eg, thyroid) disorders.

This patient has **secondary amenorrhea** associated with low body weight, frequent strenuous exercise, and lanugo (fine hair indicating inadequate caloric intake), suggesting **functional hypothalamic amenorrhea** (FHA). FHA is commonly seen in competitive athletes, dancers, fashion models, and others who maintain very low body weights. The underlying pathophysiology of FHA is incompletely understood but appears to involve reduced circulating **leptin** levels as a result of diminished adipose tissue stores. The decrease in leptin levels inhibits **pulsatile gonadotropin-releasing hormone (GnRH) release** from the hypothalamus, causing decreased pituitary LH and FSH secretion, low circulating estrogen levels, and amenorrhea.

(Choice A) Like FHA, hyperprolactinemia can cause secondary amenorrhea by suppressing normal GnRH release in the hypothalamus. Affected women may also develop galactorrhea. However, this patient's low body weight, caloric restriction, and strenuous exercise regimen are more consistent with FHA.

(Choice B) Hyperthyroidism can cause irregular menses or amenorrhea, along with weight loss. However, this patient has no other features to suggest a thyroid disorder (eg, goiter, temperature intolerance, diarrhea, hair loss).

(Choices D and E) The amenorrhea in patients with FHA stems from a deficiency in hypothalamic GnRH release, rather than a problem with the pituitary or ovaries; this patient has no other features of hypopituitarism.

Educational objective:
Functional hypothalamic amenorrhea results from loss of pulsatile gonadotropin-releasing hormone release from the hypothalamus and is caused by weight loss, strenuous exercise, systemic illness, or abnormal eating habits. Loss of cyclic gonadotropin release leads to a decrease in LH and FSH secretion from the pituitary, which in turn causes low circulating estrogen levels.

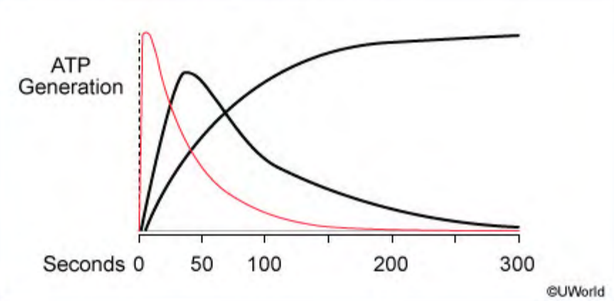
References

- Functional hypothalamic amenorrhea: current view on neuroendocrine aberrations.

Pathophysiology	Endocrine, Diabetes & Metabolism	Amenorrhea
Subject	System	Topic

https://t.me/USMLEWorldStep1

A 24-year-old, healthy woman volunteers for an exercise research study. In the study, various radiolabeled compounds are used to determine the source of skeletal muscle ATP during exercise. The participants are given carbohydrate-rich food and are asked to run on a treadmill at high speed. Which of the following is the most likely source of ATP represented by the red curve on the graph below?



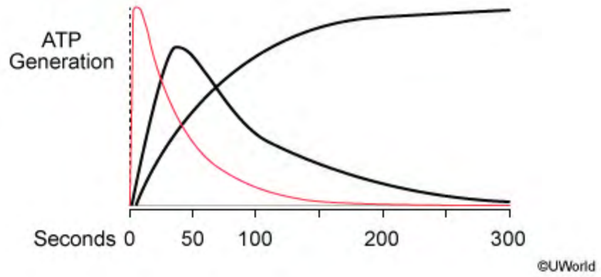
- A. Amino acids
- B. Free fatty acids
- C. Glycogen
- D. Ketone bodies
- E. Phosphocreatine

Submit

https://t.me/USMLEWorldStep1

A 24-year-old, healthy woman volunteers for an exercise research study. In the study, various radiolabeled
compo
carboh
source

Exhibit Display

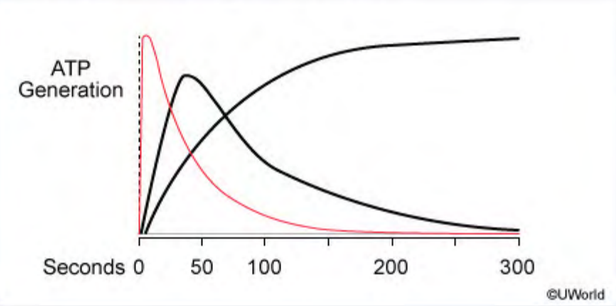


Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Sub

https://t.me/USMLEWorldStep1

A 24-year-old, healthy woman volunteers for an exercise research study. In the study, various radiolabeled compounds are used to determine the source of skeletal muscle ATP during exercise. The participants are given carbohydrate-rich food and are asked to run on a treadmill at high speed. Which of the following is the most likely source of ATP represented by the red curve on the graph below?



- A. Amino acids (3%)
- B. Free fatty acids (6%)
- ✗ C. Glycogen (42%)
- D. Ketone bodies (1%)
- ✓ E. Phosphocreatine (45%)

Incorrect
Correct answer
E

45%
Answered correctly

09 secs
Time Spent

2023
Version

Explanation

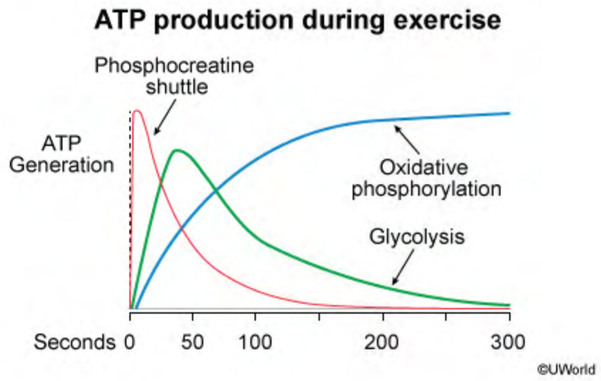
ATP production during exercise

Phosphocreatine
shuttle

https://t.me/USMLEWorldStep1

D. Ketone bodies (1%)

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Once phosphocreatine is depleted, **anaerobic glycolysis** becomes the primary source of ATP for the next stage of

https://t.me/USMLEWorldStep1

Skeletal muscle contraction requires the hydrolysis of ATP, which is only present in small amounts within the sarcoplasma. There are 3 main methods of **ATP production** during **intense exercise**, and the primary method varies with exercise duration.

The **phosphocreatine shuttle** is the primary source of ATP at the beginning (eg, **first 10 sec**) of exercise. As ATP is consumed by the muscle cell, creatine kinase removes inorganic phosphate molecules from phosphocreatine and combines them with ADP to regenerate ATP. Phosphocreatine supplies a brief burst of energy before being quickly depleted. Increased dietary intake of creatine can enhance this phase of ATP production by increasing sarcoplasmic phosphocreatine stores.

Once phosphocreatine is depleted, **anaerobic glycolysis** becomes the primary source of ATP for the next stage of exercise (eg, 10 to 60 sec). Muscle glycogen is rapidly broken down into glucose, which is converted to pyruvate (generating ATP in the process) and then lactic acid **(Choice C)**. However, the process quickly becomes limited by reduced sarcoplasmic pH caused by the accumulation of lactic acid.

Oxidative phosphorylation is the slowest of the 3 sources to reach peak production, but it is the most efficient generator of ATP and serves as the primary energy source for the remainder of exercise (eg, >60 sec). Pyruvate generated during glycolysis along with free fatty acids taken up from the circulation are converted to acetyl-coenzyme A, which is catabolized within the citric acid cycle (Krebs cycle) **(Choice B)**. This process produces NADH and $FADH_2$, which then enter the electron transport chain, where electrons are transferred to oxygen and large quantities of ATP are generated.

(Choices A and D) Amino acids and ketone bodies are sometimes used as an energy source for oxidative phosphorylation but only after glycogen and free fatty acid stores are depleted. Because amino acids are derived from muscle protein, their use as an energy source leads to muscle breakdown.

Educational objective:
Intense exercise creates a high demand for ATP, and the primary method of ATP production varies with the duration of exercise. The phosphocreatine shuttle is the primary source of ATP at the beginning of exercise, followed sequentially by anaerobic glycolysis and then oxidative phosphorylation.

https://t.me/USMLEWorldStep1

Skeletal muscle contraction requires the hydrolysis of ATP, which is only present in small amounts within the sarcop
varies

The **pl**
is cons
and co
quickly
sarcop

Once
exerci
(gener
reduce

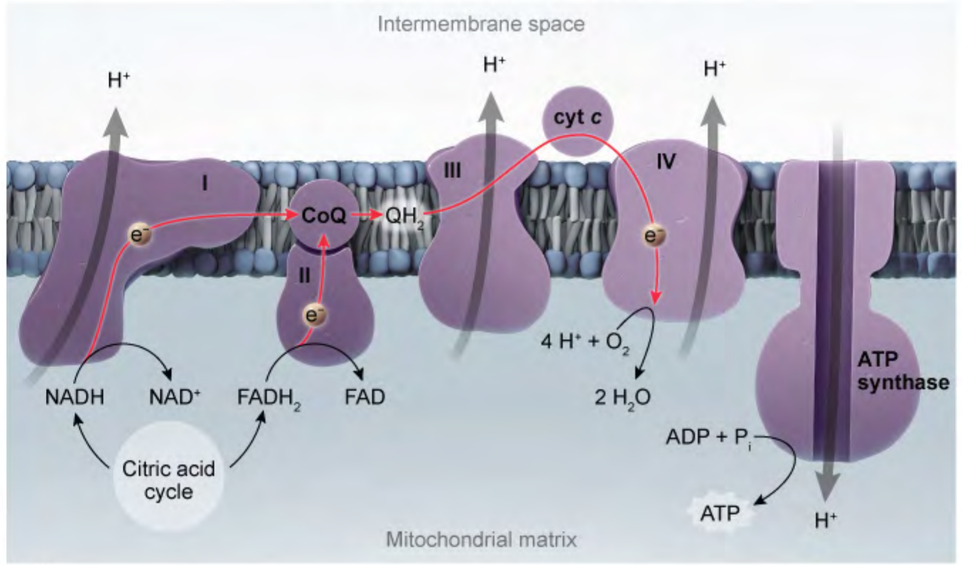
Oxida
genera
genera
coenzy
NADH
large

(Choi
phosp
from m

Educa
Intens
duratio
followed sequentially by anaerobic glycolysis and then oxidative phosphorylation.

Exhibit Display

Electron transport chain



©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

A 34-year-old man comes to the office for a follow-up visit. The patient has had type 1 diabetes since age 12 and is diligent in taking insulin to achieve good glycemic control. Over the past few months, he has had more frequent episodes of hypoglycemia despite no changes in his treatment, diet, or physical activity, but the episodes have been associated with less severe hypoglycemic symptoms compared to prior episodes. Physical examination is unremarkable. Laboratory results show normal basic metabolic panel and serum TSH level. Hemoglobin A1c is 7.0%. Which of the following factors is primarily responsible for this patient's increased frequency of hypoglycemia?

- A. Decreased epinephrine release
- B. Decreased glucagon release
- C. Decreased growth hormone release
- D. Downregulation of insulin receptors
- E. Upregulation of beta-adrenergic receptors

Submit

https://t.me/USMLEWorldStep1

A 34-year-old man comes to the office for a follow-up visit. The patient has had type 1 diabetes since age 12 and is diligent in taking insulin to achieve good glycemic control. Over the past few months, he has had more frequent episodes of hypoglycemia despite no changes in his treatment, diet, or physical activity, but the episodes have been associated with less severe hypoglycemic symptoms compared to prior episodes. Physical examination is unremarkable. Laboratory results show normal basic metabolic panel and serum TSH level. Hemoglobin A1c is 7.0%. Which of the following factors is primarily responsible for this patient's increased frequency of hypoglycemia?

- A. Decreased epinephrine release (9%)
- ✓ B. Decreased glucagon release (38%)
- C. Decreased growth hormone release (12%)
- D. Downregulation of insulin receptors (19%)
- E. Upregulation of beta-adrenergic receptors (20%)

Correct

38%
Answered correctly

04 secs
Time Spent

2023
Version

Explanation

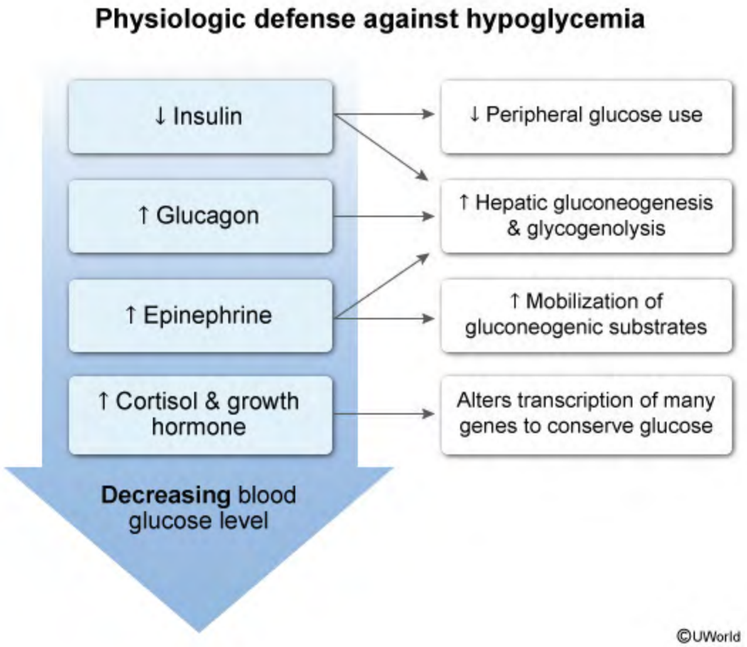
Physiologic defense against hypoglycemia



https://t.me/USMLEWorldStep1

E. Upregulation of beta-adrenergic receptors (20%)

Exhibit Display



Zoom In Zoom Out Reset New | Existing My Notebook

glycogenolysis and gluconeogenesis and decrease glycolysis.

https://t.me/USMLEWorldStep1

As blood glucose levels fall through the physiologic range, insulin secretion by pancreatic beta cells decreases, leading to reduced peripheral uptake and utilization of glucose. At the same time, alpha cells increase secretion of **glucagon**, which is the **primary counterregulatory hormone** to insulin and acts on the liver to rapidly increase glycogenolysis and gluconeogenesis and decrease glycolysis.

Patients with **type 1 diabetes mellitus** are at increased **risk of hypoglycemia** because **exogenous insulin** is not subject to the same regulation as endogenous insulin and will continue to be absorbed from the injection site despite falling glucose levels. Those with long-standing diabetes (ie, >5 years) frequently also have **alpha cell failure** with **decreased glucagon secretion** and therefore have an even greater risk of rapid hypoglycemia. Patients with pancreatogenic diabetes (eg, secondary to chronic pancreatitis) also typically have inadequate alpha cell reserve and can experience frequent hypoglycemia.

(Choice A) Progressive hypoglycemia prompts a catecholamine (eg, epinephrine) surge, which increases hepatic glucose production and triggers many of the characteristic hypoglycemic symptoms (eg, arousal, tremor). Patients with long-standing diabetes often have a blunted autonomic response to hypoglycemia, with **reduced hypoglycemic awareness**, but catecholamines are less important than glucagon in raising blood glucose levels.

(Choice C) Prolonged hypoglycemia can stimulate secretion of cortisol and growth hormone, which increase glucose levels. These hormones typically act over longer timescales (eg, days/weeks) and are less important than glucagon in preventing acute hypoglycemia.

(Choice D) Chronic exposure to high circulating insulin levels leads to downregulation of insulin receptors and reduced insulin sensitivity. This effect promotes hyperglycemia, not hypoglycemia.

(Choice E) Repeated hypoglycemia causes downregulation of beta-adrenergic receptors, which contributes to reduced hypoglycemic awareness. Depending on the systems involved, upregulation of beta-adrenergic receptors would generally reduce hypoglycemia and increase awareness.

Educational objective:
Patients with type 1 diabetes mellitus are at increased risk of hypoglycemia because exogenous insulin will continue to be absorbed from the injection site despite falling glucose levels. Those with long-standing diabetes may also have decreased glucagon secretion and therefore have an even greater risk of rapid hypoglycemia.

https://t.me/USMLEWorldStep1

A 53-year-old woman comes to the physician for a routine check-up. She has no current complaints. Her past medical history is significant for osteoarthritis of the right knee. Her mother suffered from hypertension and was diagnosed with breast cancer at age 68, from which she died 4 years later. Her father had diabetes mellitus and died in a motor vehicle accident at age 56. The patient's blood pressure is 140/85 mm Hg and heart rate is 80/min. Physical examination is normal. Laboratory testing is significant for a fasting blood glucose level of 140 mg/dL on more than 2 occasions. This patient is most likely to die from which of the following conditions?

- A. Breast cancer
- B. Hyperosmolar nonketotic coma
- C. Myocardial infarction
- D. Renal failure
- E. Stroke

Submit

https://t.me/USMLEWorldStep1

A 53-year-old woman comes to the physician for a routine check-up. She has no current complaints. Her past medical history is significant for osteoarthritis of the right knee. Her mother suffered from hypertension and was diagnosed with breast cancer at age 68, from which she died 4 years later. Her father had diabetes mellitus and died in a motor vehicle accident at age 56. The patient's blood pressure is 140/85 mm Hg and heart rate is 80/min. Physical examination is normal. Laboratory testing is significant for a fasting blood glucose level of 140 mg/dL on more than 2 occasions. This patient is most likely to die from which of the following conditions?

- A. Breast cancer (6%)
- ✗ B. Hyperosmolar nonketotic coma (3%)
- ✓ C. Myocardial infarction (61%)
- D. Renal failure (23%)
- E. Stroke (5%)

Incorrect
Correct answer
C

61%
Answered correctly

04 secs
Time Spent

2023
Version

Explanation

Risk factors for coronary heart disease	
Highest risk factors (coronary heart disease equivalents)	• Noncoronary atherosclerotic disease • Diabetes mellitus • Chronic kidney disease

https://t.me/USMLEWorldStep1

Risk factors for coronary heart disease	
Highest risk factors (coronary heart disease equivalents)	• Noncoronary atherosclerotic disease • Diabetes mellitus • Chronic kidney disease
Major risk factors	• Hypertension • Hyperlipidemia (↑ LDL & triglycerides) • Cigarette smoking • Advanced age • Obesity • Physical inactivity

Several studies have shown that diabetes mellitus is one of the strongest risk factors for coronary heart disease. Cardiovascular mortality is increased by 2- to 4-fold in patients with type 2 diabetes mellitus, and approximately 40% of patients die secondary to coronary heart disease. For a person with type 2 diabetes mellitus, the risk of dying from coronary heart disease exceeds the risk of dying from any of the other listed causes, even in the absence of other major risk factors for coronary heart disease.

(Choice A) The risk of breast cancer is not increased in patients with diabetes mellitus. Although this patient has a family history of breast cancer, her risk is not significantly increased since her mother was at an advanced age when the cancer occurred.

(Choice B) Diabetic ketoacidosis (DKA) and hyperosmolar coma are acute complications of untreated diabetes mellitus. Hyperosmolar coma is seen mainly with type 2 diabetes mellitus and is characterized by very high blood sugar levels without ketoacidosis. The mortality of hyperosmolar coma is higher than DKA; however, very few patients with diabetes die directly from DKA or hyperosmolar coma.

https://t.me/USMLEWorldStep1

	• Obesity • Physical inactivity

Several studies have shown that diabetes mellitus is one of the strongest risk factors for coronary heart disease. Cardiovascular mortality is increased by 2- to 4-fold in patients with type 2 diabetes mellitus, and approximately 40% of patients die secondary to coronary heart disease. For a person with type 2 diabetes mellitus, the risk of dying from coronary heart disease exceeds the risk of dying from any of the other listed causes, even in the absence of other major risk factors for coronary heart disease.

(Choice A) The risk of breast cancer is not increased in patients with diabetes mellitus. Although this patient has a family history of breast cancer, her risk is not significantly increased since her mother was at an advanced age when the cancer occurred.

(Choice B) Diabetic ketoacidosis (DKA) and hyperosmolar coma are acute complications of untreated diabetes mellitus. Hyperosmolar coma is seen mainly with type 2 diabetes mellitus and is characterized by very high blood sugar levels without ketoacidosis. The mortality of hyperosmolar coma is higher than DKA; however, very few patients with diabetes die directly from DKA or hyperosmolar coma.

(Choice D) Diabetes mellitus is the leading cause of end-stage renal disease (ESRD), followed by hypertension. However, approximately 50% of patients with ESRD die due to cardiovascular disease, with infections being the next most common cause.

(Choice E) The risk of stroke is increased in patients with diabetes mellitus. However, cerebrovascular accidents account for about 10% of total mortality in patients with type 2 diabetes mellitus versus 40% from coronary heart disease.

Educational objective:
Patients with **noncoronary atherosclerotic disease**, **diabetes mellitus**, or **chronic kidney disease** are at the same risk of cardiovascular events (eg, myocardial infarction, stroke) as patients with known coronary heart disease. Coronary heart disease is the most common cause of death in patients with diabetes mellitus.

Pathology	Endocrine, Diabetes & Metabolism	Diabetes mellitus
Subject	System	Topic

https://t.me/USMLEWorldStep1

A 29-year-old man comes to the office due to progressive headaches, fatigue, and visual disturbances for the past 6 weeks. He was diagnosed with sarcoidosis a year ago after having a dry cough and hypercalcemia. The patient's condition was treated with oral glucocorticoid therapy, which was discontinued after 6 months due to improvement in symptoms. Physical examination reveals bitemporal defects on visual field testing but is otherwise normal. Laboratory studies again show mild hypercalcemia, but the remainder of the values, including complete blood count, serum glucose, creatinine, and electrolytes, are within normal reference ranges. MRI of the brain reveals a soft tissue mass involving the hypothalamus and pituitary stalk. Which of the following pituitary hormones is most likely elevated in this patient?

- A. ACTH
- B. Growth hormone
- C. Prolactin
- D. Thyrotropin
- E. Vasopressin

Submit

https://t.me/USMLEWorldStep1

A 29-year-old man comes to the office due to progressive headaches, fatigue, and visual disturbances for the past 6 weeks. He was diagnosed with sarcoidosis a year ago after having a dry cough and hypercalcemia. The patient's condition was treated with oral glucocorticoid therapy, which was discontinued after 6 months due to improvement in symptoms. Physical examination reveals bitemporal defects on visual field testing but is otherwise normal. Laboratory studies again show mild hypercalcemia, but the remainder of the values, including complete blood count, serum glucose, creatinine, and electrolytes, are within normal reference ranges. MRI of the brain reveals a soft tissue mass involving the hypothalamus and pituitary stalk. Which of the following pituitary hormones is most likely elevated in this patient?

- ✗ A. ACTH (13%)
- B. Growth hormone (3%)
- ✓ C. Prolactin (67%)
- D. Thyrotropin (6%)
- E. Vasopressin (8%)

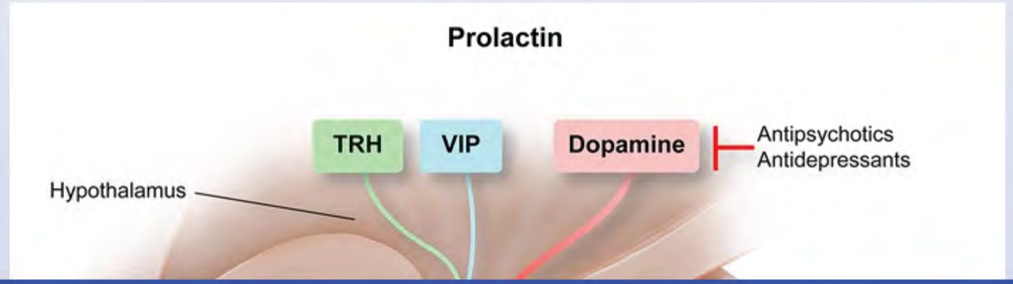
Incorrect
Correct answer
C

67%
Answered correctly

04 secs
Time Spent

2023
Version

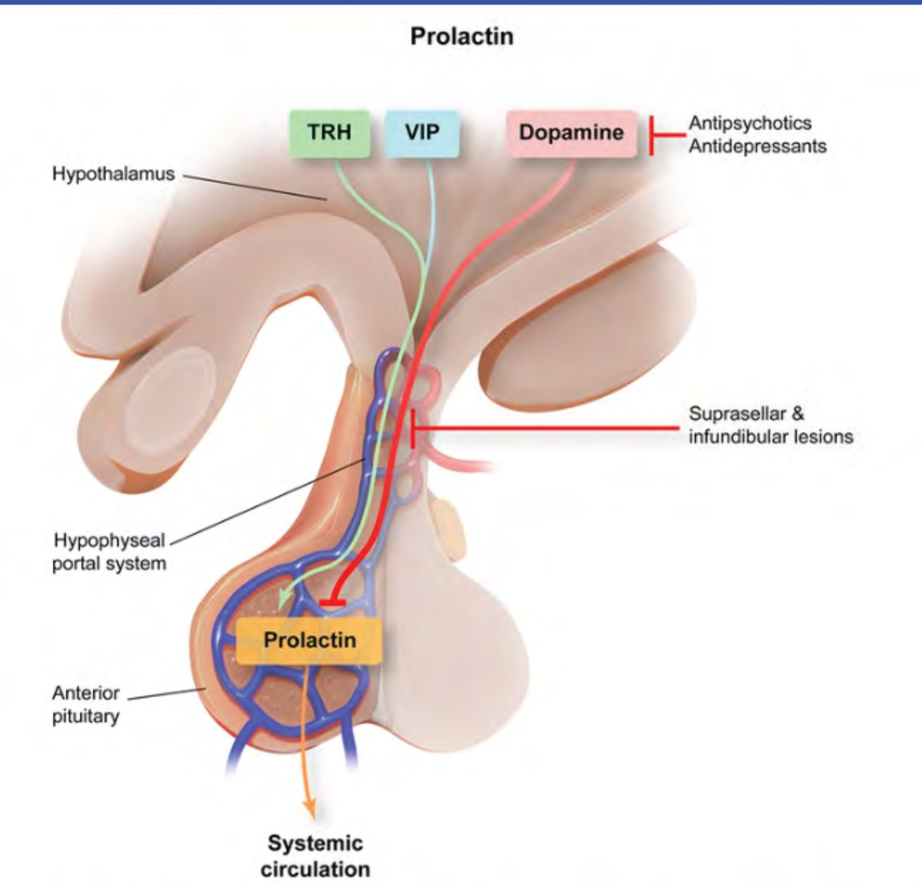
Explanation



https://t.me/USMLEWorldStep1

A 29-year-old man comes to the office due to progressive headaches, fatigue, and visual disturbances for the past 6 wee
patien
improv
norma
blood
reveal
hormo

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

TRH = thyrotropin-releasing hormone; **VIP** = vasoactive intestinal peptide.

©UWorld

This patient with **sarcoidosis** has a hypothalamic and pituitary stalk mass with **mass-effect symptoms** (eg, headache, bitemporal visual field defects). In combination with the recurrent hypercalcemia (caused by excessive calcitriol formation by activated macrophages) 6 months after the discontinuation of glucocorticoid therapy, this presentation suggests active sarcoidosis with involvement of the hypothalamus (**neurosarcoidosis**). Although sarcoidosis classically causes noncaseating granulomas involving the lungs, lymph nodes, and skin, granulomas can form in any tissue.

Mass lesions in the hypothalamus or pituitary stalk can disrupt the hypothalamic-pituitary axis by obstructing the hypophyseal portal system. Unlike other pituitary hormones, **prolactin** release is **negatively regulated by dopamine** produced in the hypothalamus. Dopamine acts on the dopamine D2 receptors of lactotrophs, the prolactin-producing cells of the pituitary. Disruption of dopaminergic pathways (eg, by an infiltrating sarcoid lesion) in the pituitary stalk leads to **loss of inhibition** and a subsequent **increase in prolactin**.

(Choices A, B, and D) Pituitary adenomas can cause excess hormone formation; however, this patient has a hypothalamic mass, not a pituitary adenoma. In contrast to prolactin, other pituitary hormones (ACTH, growth hormone, thyrotropin [TSH], LH, and FSH) are inhibited by hypothalamic lesions because the dominant effect of the hypothalamus on them is stimulatory. Although abruptly discontinuing an oral glucocorticoid can cause adrenal insufficiency with a subsequent increase in ACTH, low blood pressure, hypoglycemia, hyponatremia, and hyperkalemia would be expected. In addition, adrenal insufficiency typically occurs rapidly after glucocorticoid withdrawal (not 6 months later).

(Choice E) Vasopressin is produced in the supraoptic and paraventricular nuclei of the hypothalamus and transported to the posterior pituitary for release. Lesions of the hypothalamus and pituitary stalk can decrease vasopressin levels. Mass lesions in the central nervous system can cause vasopressin secretory dysregulation, leading to the syndrome of inappropriate antidiuretic hormone (SIADH) with euvolemic hyponatremia. However, the normal sodium levels in this patient exclude this syndrome.

Educational objective:
The release of prolactin is under inhibitory control by dopamine secretion from the hypothalamus. Disruption of dopaminergic pathways or blockade of dopamine D2 receptors can cause hyperprolactinemia.

https://t.me/USMLEWorldStep1

A newborn boy is found to have elevated TSH and low thyroxine (T4) levels on routine newborn screening. The patient was born vaginally to a 32-year-old, healthy woman at 39 weeks gestation. The 5-minute Apgar score was 9. Ultrasound of the neck reveals an ectopically located, small thyroid gland just above the hyoid bone. Early treatment with levothyroxine is indicated primarily to prevent which of the following?

- A. Excessive weight gain
- B. Neurocognitive dysfunction
- C. Nutrient malabsorption
- D. Proptosis
- E. Thyroid gland enlargement

Submit

https://t.me/USMLEWorldStep1

A newborn boy is found to have elevated TSH and low thyroxine (T4) levels on routine newborn screening. The patient was born vaginally to a 32-year-old, healthy woman at 39 weeks gestation. The 5-minute Apgar score was 9. Ultrasound of the neck reveals an ectopically located, small thyroid gland just above the hyoid bone. Early treatment with levothyroxine is indicated primarily to prevent which of the following?

- A. Excessive weight gain (3%)
- ✓ B. Neurocognitive dysfunction (80%)
- C. Nutrient malabsorption (2%)
- D. Proptosis (1%)
- E. Thyroid gland enlargement (12%)

Correct | 80% Answered correctly | 04 secs Time Spent | 2023 Version

Explanation

Congenital hypothyroidism	
Clinical manifestations	• Asymptomatic at birth • After maternal thyroxine wanes (weeks to months): ◦ Lethargy, poor feeding ◦ Enlarged fontanelle ◦ Protruding tongue, puffy face, umbilical hernia ◦ Constipation ◦ Prolonged jaundice ◦ Dry skin

https://t.me/USMLEWorldStep1

Congenital hypothyroidism	
Clinical manifestations	• Asymptomatic at birth • After maternal thyroxine wanes (weeks to months): ◦ Lethargy, poor feeding ◦ Enlarged fontanelle ◦ Protruding tongue, puffy face, umbilical hernia ◦ Constipation ◦ Prolonged jaundice ◦ Dry skin
Diagnosis	• ↑ TSH & ↓ free thyroxine levels • Newborn screening
Treatment	• Levothyroxine*
*Delayed treatment is associated with neurocognitive dysfunction (eg, ↓ intelligence quotient).	

This newborn with elevated TSH and low thyroxine (T4) has **congenital hypothyroidism** due to failed thyroid gland migration. **Ectopic thyroid** tissue typically produces inadequate levels of T4, a hormone critical to the metabolism, growth, and development of the fetus and young child.

Newborns with congenital hypothyroidism are usually asymptomatic due to transplacental transfer of small amounts of maternal T4 that prevent development of overt symptoms. As such, most infants are identified via **routine newborn screening**. Prompt initiation of treatment with **levothyroxine** (ie, thyroid hormone supplementation) before maternally derived T4 wanes (weeks to months after birth) is associated with an **excellent prognosis** and no long-term deficits.

In contrast, **untreated** or inadequately treated hypothyroidism in the first few years of life is associated with **neurocognitive dysfunction**. These patients typically have **lower intelligence quotients** (IQs) compared to those with appropriately treated hypothyroidism. Severe, untreated hypothyroidism may also lead to **neurologic**

https://t.me/USMLEWorldStep1

This newborn with elevated TSH and low thyroxine (T4) has **congenital hypothyroidism** due to failed thyroid gland migration. **Ectopic thyroid** tissue typically produces inadequate levels of T4, a hormone critical to the metabolism, growth, and development of the fetus and young child.

Newborns with congenital hypothyroidism are usually asymptomatic due to transplacental transfer of small amounts of maternal T4 that prevent development of overt symptoms. As such, most infants are identified via **routine newborn screening**. Prompt initiation of treatment with **levothyroxine** (ie, thyroid hormone supplementation) before maternally derived T4 wanes (weeks to months after birth) is associated with an **excellent prognosis** and no long-term deficits.

In contrast, **untreated** or inadequately treated hypothyroidism in the first few years of life is associated with **neurocognitive dysfunction**. These patients typically have **lower intelligence quotients** (IQs) compared to those with appropriately treated hypothyroidism. Severe, untreated hypothyroidism may also lead to **neurologic deficits** (eg, sensorineural hearing loss, poor coordination). Of note, pregnant women inadequately treated for hypothyroidism are at increased risk of having a child with a decreased IQ because the developing fetus depends solely on maternal T4 during early gestation.

(Choices A and E) Elevated TSH associated with untreated hypothyroidism leads to thyroid gland overstimulation and, often, enlargement (ie, goiter). Myxedema (due to glycosaminoglycan accumulation) and a decreased metabolic rate can cause excessive weight gain in untreated disease. However, in contrast to irreversible neurocognitive dysfunction, preventing these largely reversible manifestations of hypothyroidism are not the primary goals of therapy.

(Choice C) Some autoimmune diseases, such as celiac disease and pernicious anemia, are more common in patients with hypothyroidism, and are associated with nutrient loss due to malabsorption. Treatment of hypothyroidism does not decrease the risk for these conditions, and hypothyroidism alone does not cause malabsorption.

(Choice D) Proptosis occurs with untreated Graves' hyperthyroidism, not hypothyroidism, due to extraocular muscle swelling and orbital edema. In contrast to this case, hyperthyroidism is characterized by low TSH and high T4.

Educational objective:

https://t.me/USMLEWorldStep1

Newborns with congenital hypothyroidism are usually asymptomatic due to transplacental transfer of small amounts of maternal T4 that prevent development of overt symptoms. As such, most infants are identified via **routine newborn screening**. Prompt initiation of treatment with **levothyroxine** (ie, thyroid hormone supplementation) before maternally derived T4 wanes (weeks to months after birth) is associated with an **excellent prognosis** and no long-term deficits.

In contrast, **untreated** or inadequately treated hypothyroidism in the first few years of life is associated with **neurocognitive dysfunction**. These patients typically have **lower intelligence quotients** (IQs) compared to those with appropriately treated hypothyroidism. Severe, untreated hypothyroidism may also lead to **neurologic deficits** (eg, sensorineural hearing loss, poor coordination). Of note, pregnant women inadequately treated for hypothyroidism are at increased risk of having a child with a decreased IQ because the developing fetus depends solely on maternal T4 during early gestation.

(Choices A and E) Elevated TSH associated with untreated hypothyroidism leads to thyroid gland overstimulation and, often, enlargement (ie, goiter). Myxedema (due to glycosaminoglycan accumulation) and a decreased metabolic rate can cause excessive weight gain in untreated disease. However, in contrast to irreversible neurocognitive dysfunction, preventing these largely reversible manifestations of hypothyroidism are not the primary goals of therapy.

(Choice C) Some autoimmune diseases, such as celiac disease and pernicious anemia, are more common in patients with hypothyroidism, and are associated with nutrient loss due to malabsorption. Treatment of hypothyroidism does not decrease the risk for these conditions, and hypothyroidism alone does not cause malabsorption.

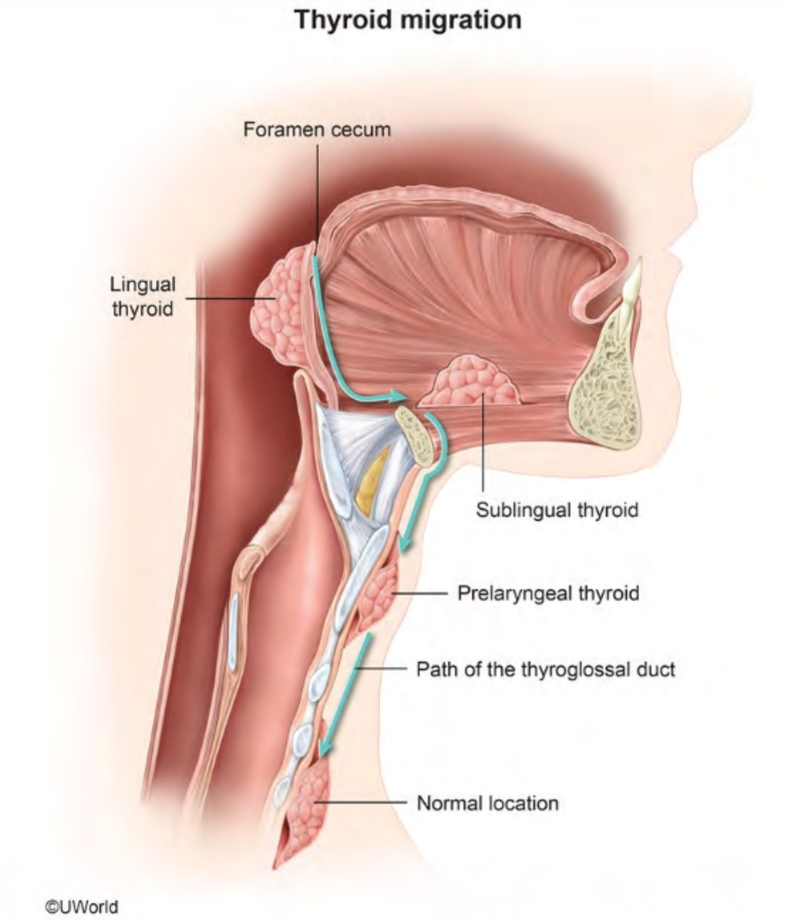
(Choice D) Proptosis occurs with untreated Graves' hyperthyroidism, not hypothyroidism, due to extraocular muscle swelling and orbital edema. In contrast to this case, hyperthyroidism is characterized by low TSH and high T4.

Educational objective:
Congenital hypothyroidism is treated with prompt initiation of levothyroxine in early infancy. Late or inadequate treatment is associated with cognitive (ie, lower intelligence quotient) and neurologic (eg, hearing loss, incoordination) dysfunction.

https://t.me/USMLEWorldStep1

- Dry skin

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

This n
gland
metab

Newbo
amour
via **rou**
supple
progn

In con
neuro
those
deficit
hypoth
solely

(Choic
and, o
metab
neuroc
primar

(Choice C) Some autoimmune diseases, such as celiac disease and pernicious anemia, are more common in

https://t.me/USMLEWorldStep1

The following vignette applies to the next **2** items. The items in the set must be answered in sequential order. Once you click **Proceed to Next Item**, you will not be able to add or change an answer.

A 4-year-old boy is brought to the clinic after his mother noticed he was developing pubic hair. The boy had a recent growth spurt and is now taller than his 5-year-old brother. The patient's preschool teacher recently mentioned he has body odor after he runs or plays. Height is at the 95th percentile for age, and weight is at the 80th percentile. Examination reveals sparse growth of long, pigmented hair at the base of the penis and in both axillae. Testes are present bilaterally and appear normal. Laboratory assessment reveals high serum concentrations of 17-hydroxyprogesterone and testosterone.

Item 1 of 2

Which of the following is most likely present in this patient?

- A. Adrenal cortical hyperplasia
- B. Adrenal medullary hyperplasia
- C. Leydig cell tumor
- D. Pituitary adenoma
- E. Seminoma

Submit

https://t.me/USMLEWorldStep1

Item 2 of 2

After initial assessment, the appropriate interventions are initiated. Targeted suppression of which of the following hormones is the best next step to limit androgen overproduction?

- A. Adrenocorticotropic hormone
- B. Cortisol
- C. Luteinizing hormone
- D. Prolactin
- E. Testosterone

Submit

https://t.me/USMLEWorldStep1

The following vignette applies to the next **2** items. The items in the set must be answered in sequential order. Once you click **Proceed to Next Item**, you will not be able to add or change an answer.

A 4-year-old boy is brought to the clinic after his mother noticed he was developing pubic hair. The boy had a recent growth spurt and is now taller than his 5-year-old brother. The patient's preschool teacher recently mentioned he has body odor after he runs or plays. Height is at the 95th percentile for age, and weight is at the 80th percentile. Examination reveals sparse growth of long, pigmented hair at the base of the penis and in both axillae. Testes are present bilaterally and appear normal. Laboratory assessment reveals high serum concentrations of 17-hydroxyprogesterone and testosterone.

Item 1 of 2

Which of the following is most likely present in this patient?

- ✓ A. Adrenal cortical hyperplasia (79%)
- B. Adrenal medullary hyperplasia (4%)
- C. Leydig cell tumor (8%)
- D. Pituitary adenoma (7%)
- E. Seminoma (0%)

Correct

79% Answered correctly

42 secs Time Spent

2023 Version

Explanation

21-Hydroxylase deficiency clinical syndromes			
	Classic,	**Classic,**	**Nonclassic,**

https://t.me/USMLEWorldStep1

Explanation

21-Hydroxylase deficiency clinical syndromes			
	Classic, salt wasting	**Classic, non–salt wasting***	**Nonclassic, late onset**
Enzyme deficiency	Severe	Moderate	Mild
Clinical features	• Birth (girls): ambiguous genitalia • Age 1-2 weeks: vomiting, hypotension, hyperkalemia	• Birth (girls): ambiguous genitalia • Age 2-4: virilization (eg, body odor, pubic/axillary hair) & rapid growth	• School-aged: premature pubarche & rapid growth • Adolescence (girls): hirsutism, acne, oligomenorrhea
Laboratory features	• Increased 17-hydroxyprogesterone • Increased testosterone		
*Also called simple virilizing form.			

Deficiency of 21-hydroxylase is the most common form of **congenital adrenal hyperplasia** and leads to impaired conversion of 17-hydroxyprogesterone (17-OHP) to 11-deoxycortisol. Excess 17-OHP is shunted away from cortisol synthesis toward androgen production. **ACTH increases** due to the decline in cortisol levels and has a trophic effect on adrenal cortical cells, causing **adrenal cortical hyperplasia**.

Depending on the residual enzyme activity, 21-hydroxylase deficiency can present as 3 distinct clinical syndromes of differing severity. This patient most likely has the **classic, non–salt-wasting** (ie, simple virilizing) form of the disease. Because 21-hydroxylase is not completely absent (as in the most severe form), sufficient mineralocorticoids and glucocorticoids are maintained to avoid salt wasting such that patients have normal blood pressure and electrolytes. Due to **adrenal androgen overproduction**, girls with this variant are often identified at birth due to ambiguous genitalia. **Boys** appear normal at birth and typically present around **age 2-4** with **early**

https://t.me/USMLEWorldStep1

Enzyme deficiency	Severe	Moderate	Mild
Clinical features	• Birth (girls): ambiguous genitalia • Age 1-2 weeks: vomiting, hypotension, hyperkalemia	• Birth (girls): ambiguous genitalia • Age 2-4: virilization (eg, body odor, pubic/axillary hair) & rapid growth	• School-aged: premature pubarche & rapid growth • Adolescence (girls): hirsutism, acne, oligomenorrhea
Laboratory features	• Increased 17-hydroxyprogesterone • Increased testosterone		
*Also called simple virilizing form.			

Deficiency of 21-hydroxylase is the most common form of **congenital adrenal hyperplasia** and leads to impaired conversion of 17-hydroxyprogesterone (17-OHP) to 11-deoxycortisol. Excess 17-OHP is shunted away from cortisol synthesis toward androgen production. **ACTH increases** due to the decline in cortisol levels and has a trophic effect on adrenal cortical cells, causing **adrenal cortical hyperplasia**.

Depending on the residual enzyme activity, 21-hydroxylase deficiency can present as 3 distinct clinical syndromes of differing severity. This patient most likely has the **classic, non–salt-wasting** (ie, simple virilizing) form of the disease. Because 21-hydroxylase is not completely absent (as in the most severe form), sufficient mineralocorticoids and glucocorticoids are maintained to avoid salt wasting such that patients have normal blood pressure and electrolytes. Due to **adrenal androgen overproduction**, girls with this variant are often identified at birth due to ambiguous genitalia. **Boys** appear normal at birth and typically present around **age 2-4** with **early virilization** (eg, body odor, pubic/axillary hair). Exposure to high levels of sex hormones also induces an early pubertal growth spurt that manifests as **accelerated linear growth** at a young age.

In all forms of 21-hydroxylase deficiency, patients have **increased 17-OHP** and androgen levels. Adrenal androgens (eg, dehydroepiandrosterone and androstenedione) undergo peripheral conversion to testosterone, which explains this patient's **high testosterone** level.

(Choice B) Adrenal medullary hyperplasia is a precursor lesion for pheochromocytoma characterized by

https://t.me/USMLEWorldStep1

of differing severity. This patient most likely has the **classic, non–salt-wasting** (ie, simple virilizing) form of the disease. Because 21-hydroxylase is not completely absent (as in the most severe form), sufficient mineralocorticoids and glucocorticoids are maintained to avoid salt wasting such that patients have normal blood pressure and electrolytes. Due to **adrenal androgen overproduction**, girls with this variant are often identified at birth due to ambiguous genitalia. **Boys** appear normal at birth and typically present around **age 2-4** with **early virilization** (eg, body odor, pubic/axillary hair). Exposure to high levels of sex hormones also induces an early pubertal growth spurt that manifests as **accelerated linear growth** at a young age.

In all forms of 21-hydroxylase deficiency, patients have **increased 17-OHP** and androgen levels. Adrenal androgens (eg, dehydroepiandrosterone and androstenedione) undergo peripheral conversion to testosterone, which explains this patient's **high testosterone** level.

(Choice B) Adrenal medullary hyperplasia is a precursor lesion for pheochromocytoma characterized by increased catecholamine production. Presenting signs include hypertension, tachycardia, and sweating (not virilization).

(Choice C) Leydig cell tumors produce excess testosterone and can present with precocious puberty in young boys (eg, early testicular/phallic enlargement). A testicular mass is typically palpated on examination.

(Choice D) Production of excess LH and FSH by pituitary adenomas can lead to increased testosterone but not increased 17-OHP levels. Pituitary adenomas producing excess ACTH can lead to excess adrenal androgen production; however, symptoms of excess cortisol production (Cushing syndrome) such as growth deceleration and weight gain would predominate.

(Choice E) A seminoma is a testicular tumor most commonly found in adolescents and adults. These tumors are derived from the seminiferous tubules and present with a testicular mass, not virilization and elevated testosterone.

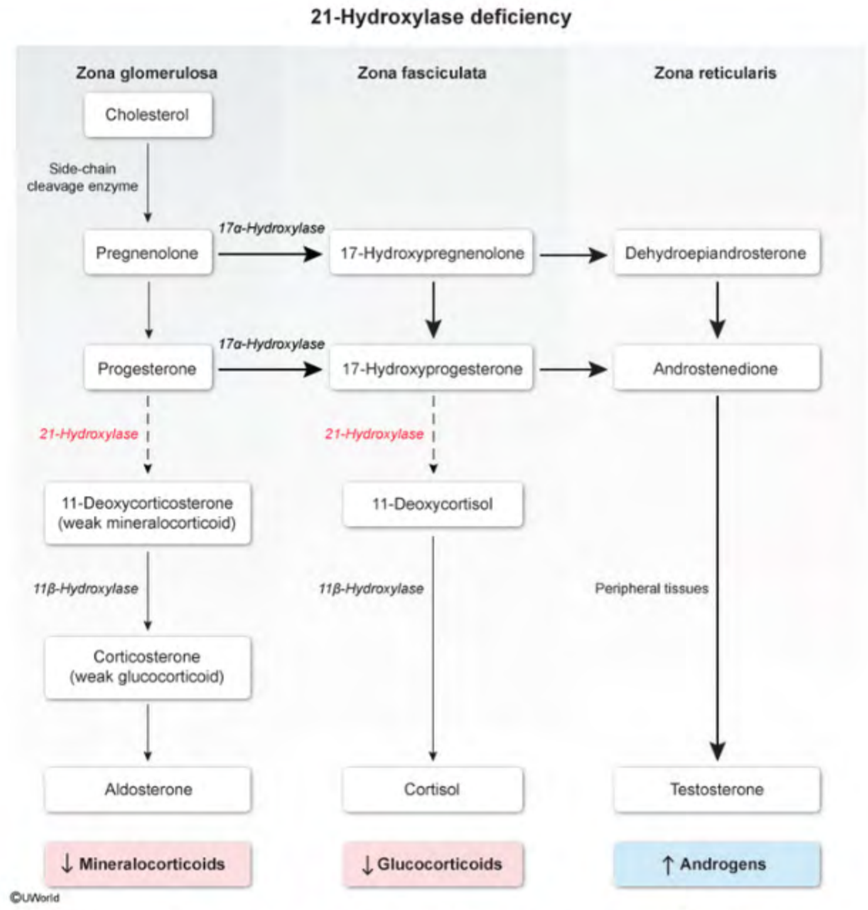
Educational objective:
Deficiency of 21-hydroxylase causes adrenal cortical hyperplasia due to excess stimulation of the adrenal cortex by ACTH. The classic, non–salt-wasting form presents in boys age 2-4 with early virilization, accelerated linear growth, and elevated levels of 17-hydroxyprogesterone and androgens.

Pathology Endocrine, Diabetes & Metabolism Congenital adrenal hyperplasia

https://t.me/USMLEWorldStep1

*Also called simple virilizing form.

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Deficie
conver
cortisc
trophic

Deper
of diffe
diseas
minera
pressu
birth d
viriliz
puberty

In all f
androg
which

(Choi
increa
viriliza

(Choi
boys (

(Choi
increa
produc
and w

(Choice E) A seminoma is a testicular tumor most commonly found in adolescents and adults. These tumors are

https://t.me/USMLEWorldStep1

Item 2 of 2

After initial assessment, the appropriate interventions are initiated. Targeted suppression of which of the following hormones is the best next step to limit androgen overproduction?

- ✓ A. Adrenocorticotropic hormone (52%)
- ✗ B. Cortisol (4%)
- C. Luteinizing hormone (21%)
- D. Prolactin (1%)
- E. Testosterone (19%)

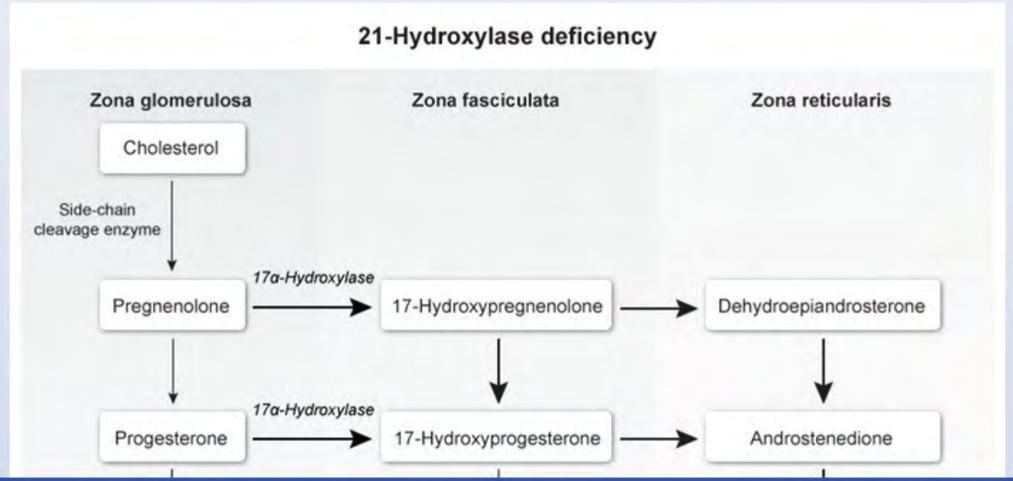
Incorrect
Correct answer
A

52%
Answered correctly

07 secs
Time Spent

2023
Version

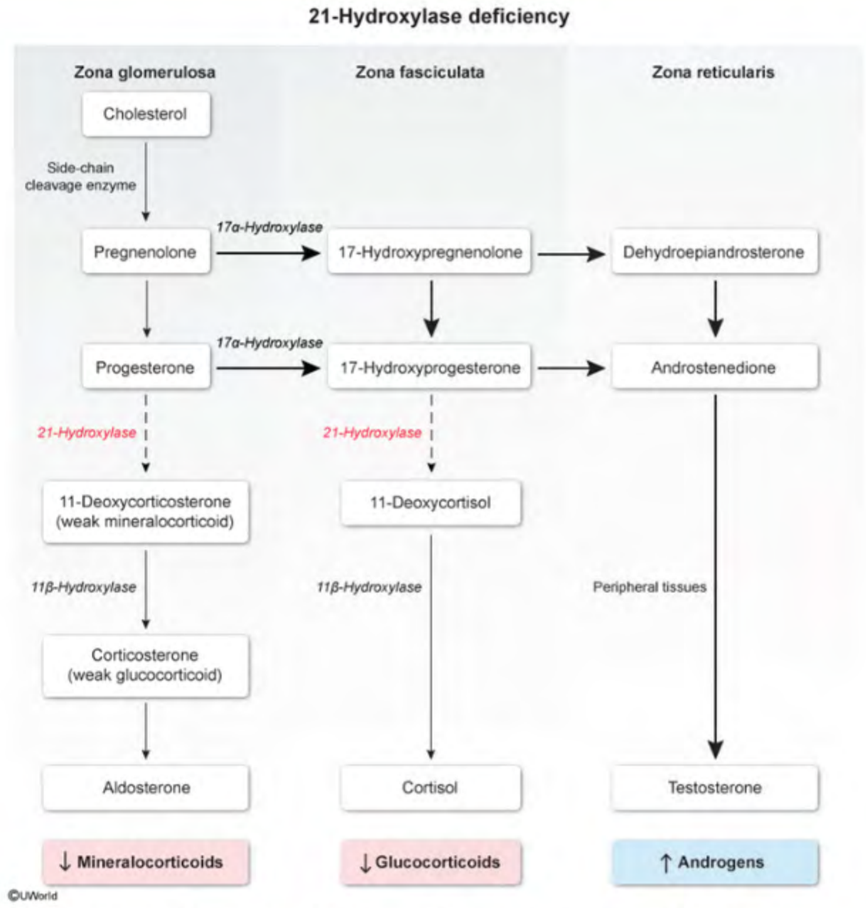
Explanation



https://t.me/USMLEWorldStep1

C. Luteinizing hormone (21%)

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1



Patients with congenital adrenal hyperplasia (CAH) due to **21-hydroxylase deficiency** have impaired cortisol synthesis. Subsequent lack of feedback causes the hypothalamus to **increase adrenocorticotropic hormone (ACTH) secretion** by the anterior pituitary. This results in stimulation of the adrenal cortex and **adrenal androgen overproduction** (eg, dehydroepiandrosterone, androstenedione).

Treatment of 21-hydroxylase deficiency involves low (ie, physiologic) doses of exogenous corticosteroids that **suppress ACTH secretion** via negative feedback mechanisms. Without excess ACTH stimulation, androgen production by the adrenal cortex decreases.

(Choice B) Deficiency of 21-hydroxylase impairs cortisol synthesis; further suppression of cortisol production could precipitate an adrenal crisis (eg, hypoglycemia, hypotension).

(Choice C) Luteinizing hormone (LH) stimulates the testes to produce testosterone. Decreasing LH levels would decrease testosterone production by the testes but would not affect excess adrenal androgen production in CAH.

(Choice D) Hyperprolactinemia disrupts GnRH secretion, which leads to decreased testosterone production and hypogonadism. Prolactin suppression would further elevate testosterone levels and would not be beneficial in this patient.

(Choice E) This patient's symptoms are the result of excessive production of adrenal androgens (eg, dehydroepiandrosterone and androstenedione), which can subsequently undergo peripheral conversion to testosterone. Blockade of testosterone alone would not be sufficient to prevent progression of this patient's symptoms, as the androgenic effects of these testosterone precursors would remain unopposed.

Educational objective:
Treatment of congenital adrenal hyperplasia due to 21-hydroxylase deficiency involves low doses of exogenous corticosteroids to suppress excess ACTH secretion, which reduces production of androgens by the adrenal cortex.

Pathology	Endocrine, Diabetes & Metabolism	Congenital adrenal hyperplasia
Subject	System	Topic

https://t.me/USMLEWorldStep1

↓ Mineralocorticoids ↓ Glucocorticoids ↑ Androgens

Exhibit Display

Patien
synthe
(ACTH
overp

Treatn
suppr
produc

(Choi
could

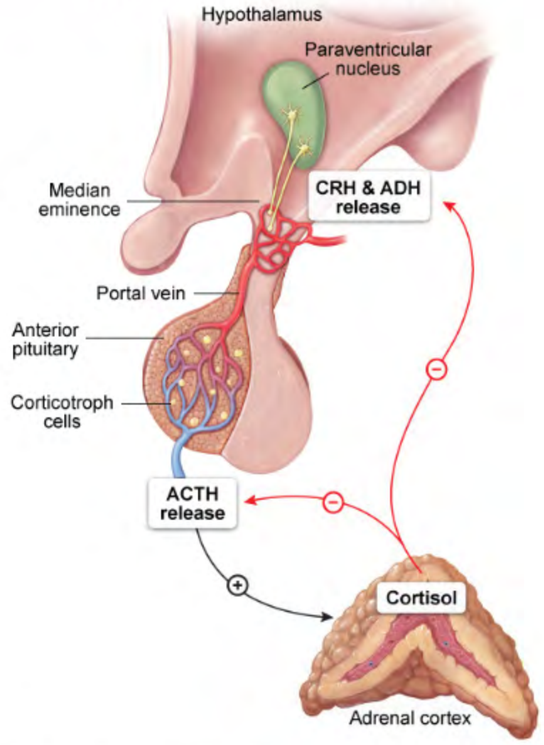
(Choi
decrea

(Choi
hypog
patien

(Choi
dehyd
testost
sympt

Educa
Treatn
cortico

Hypothalamic-pituitary-adrenal axis



ADH = antidiuretic hormone; **CRH** = corticotropin-releasing hormone.

©UWorld

Zoom In Zoom Out Reset New | Existing My Notebook

Pathology	Endocrine, Diabetes & Metabolism	Congenital adrenal hyperplasia
Subject	System	Topic

https://t.me/USMLEWorldStep1

A neonate is found to have increased TSH and low thyroxine (T4) on routine screening. He was born by vaginal delivery to a 32-year-old woman at 39 weeks gestation. Apgar scores were 8 and 9 at 1 and 5 minutes, respectively. Physical examination reveals an enlarged thyroid gland in the normal position. Neck ultrasound confirms thyroid enlargement. Which of the following is the most likely cause of this patient's findings?

- A. Maternal intake of levothyroxine
- B. Maternal intake of propranolol
- C. Maternal intake of propylthiouracil
- D. Transplacental passage of thyroglobulin
- E. Transplacental passage of TSH receptor–stimulating antibodies

Submit

https://t.me/USMLEWorldStep1

A neonate is found to have increased TSH and low thyroxine (T4) on routine screening. He was born by vaginal delivery to a 32-year-old woman at 39 weeks gestation. Apgar scores were 8 and 9 at 1 and 5 minutes, respectively. Physical examination reveals an enlarged thyroid gland in the normal position. Neck ultrasound confirms thyroid enlargement. Which of the following is the most likely cause of this patient's findings?

- A. Maternal intake of levothyroxine (13%)
- ✕ B. Maternal intake of propranolol (3%)
- ✓ C. Maternal intake of propylthiouracil (47%)
- D. Transplacental passage of thyroglobulin (11%)
- E. Transplacental passage of TSH receptor–stimulating antibodies (22%)

Incorrect
Correct answer
C

47%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

Common causes of congenital goiter

Disorder	TSH	FT4	Causes
Hypothyroidism	↑	↓	• Genetic defect in thyroid hormone production • Maternal antithyroid medication (eg, propylthiouracil) • Excessive or deficient maternal iodine
Hyperthyroidism	↓	↑	• Transplacental TSH receptor–stimulating antibodies (neonatal Graves disease)

FT4 = free thyroxine.

https://t.me/USMLEWorldStep1

Common causes of congenital goiter			
Disorder	**TSH**	**FT4**	**Causes**
Hypothyroidism	↑	↓	• Genetic defect in thyroid hormone production • Maternal antithyroid medication (eg, propylthiouracil) • Excessive or deficient maternal iodine
Hyperthyroidism	↓	↑	• Transplacental TSH receptor–stimulating antibodies (neonatal Graves disease)
FT4 = free thyroxine.			

This **neonate** has a **goiter**, or an enlarged thyroid gland, which is typically due to thyroid hormone dysregulation. The most commonly associated imbalance is **hypothyroidism**, as seen in this patient with elevated TSH and decreased thyroxine (T4).

One cause of neonatal hypothyroidism with a goiter is the **transplacental** passage of **maternal antithyroid medications** (eg, propylthiouracil, methimazole). Propylthiouracil is used to treat maternal hyperthyroidism (eg, Graves disease) because it inhibits thyroid peroxidase, thereby limiting oxidation and incorporation of iodine into thyroid hormones; this medication also decreases conversion of peripheral T4 to triiodothyronine (T3).

Propylthiouracil crosses the placenta, inhibiting production of T4. Positive feedback caused by low T4 leads to increased TSH, which stimulates the thyroid and causes **diffuse gland enlargement**. TSH and T4 levels typically normalize after 1-2 weeks due to excretion of the maternally derived antithyroid medication. After elimination of propylthiouracil, neonates with mothers who have Graves disease may then develop transient hyperthyroidism (↓ TSH, ↑ T4) due to transplacental transfer of TSH receptor–stimulating antibodies **(Choice E)**, which can persist in the neonatal circulation for up to 3 months.

(Choice A) Levothyroxine (synthetic T4), like other thyroid hormones, does not readily cross the placenta. In addition, this medication treats, not causes, hypothyroidism.

https://t.me/USMLEWorldStep1

FT4 = free thyroxine.

This **neonate** has a **goiter**, or an enlarged thyroid gland, which is typically due to thyroid hormone dysregulation. The most commonly associated imbalance is **hypothyroidism**, as seen in this patient with elevated TSH and decreased thyroxine (T4).

One cause of neonatal hypothyroidism with a goiter is the **transplacental** passage of **maternal antithyroid medications** (eg, propylthiouracil, methimazole). Propylthiouracil is used to treat maternal hyperthyroidism (eg, Graves disease) because it inhibits thyroid peroxidase, thereby limiting oxidation and incorporation of iodine into thyroid hormones; this medication also decreases conversion of peripheral T4 to triiodothyronine (T3).

Propylthiouracil crosses the placenta, inhibiting production of T4. Positive feedback caused by low T4 leads to increased TSH, which stimulates the thyroid and causes **diffuse gland enlargement**. TSH and T4 levels typically normalize after 1-2 weeks due to excretion of the maternally derived antithyroid medication. After elimination of propylthiouracil, neonates with mothers who have Graves disease may then develop transient hyperthyroidism (↓ TSH, ↑ T4) due to transplacental transfer of TSH receptor–stimulating antibodies **(Choice E)**, which can persist in the neonatal circulation for up to 3 months.

(Choice A) Levothyroxine (synthetic T4), like other thyroid hormones, does not readily cross the placenta. In addition, this medication treats, not causes, hypothyroidism.

(Choice B) Beta blockers (eg, propranolol) treat symptoms of hyperthyroidism attributable to increased beta-adrenergic activity (eg, palpitations, tachycardia). Although propranolol also decreases conversion of T4 to T3, this inhibitory effect is not strong enough to cause overt hypothyroidism and goiter at normal doses.

(Choice D) Thyroglobulin is a protein produced by the thyroid follicular cells and is involved in the storage and production of thyroid hormones. Thyroglobulin does not cross the placenta or cause hypothyroidism.

Educational objective:
Congenital goiter in the setting of hypothyroidism (ie, ↑ TSH, ↓ thyroxine) can be caused by transplacental passage of maternal antithyroid medications (eg, propylthiouracil), which inhibit thyroid peroxidase and are used to treat maternal hyperthyroidism.

References

https://t.me/USMLEWorldStep1

FT4 = free thyroxine.

This n
The m
decrea

One c
medic
Grave
thyroic

Propyl
increa
norma
propyl
TSH, 1
the ne

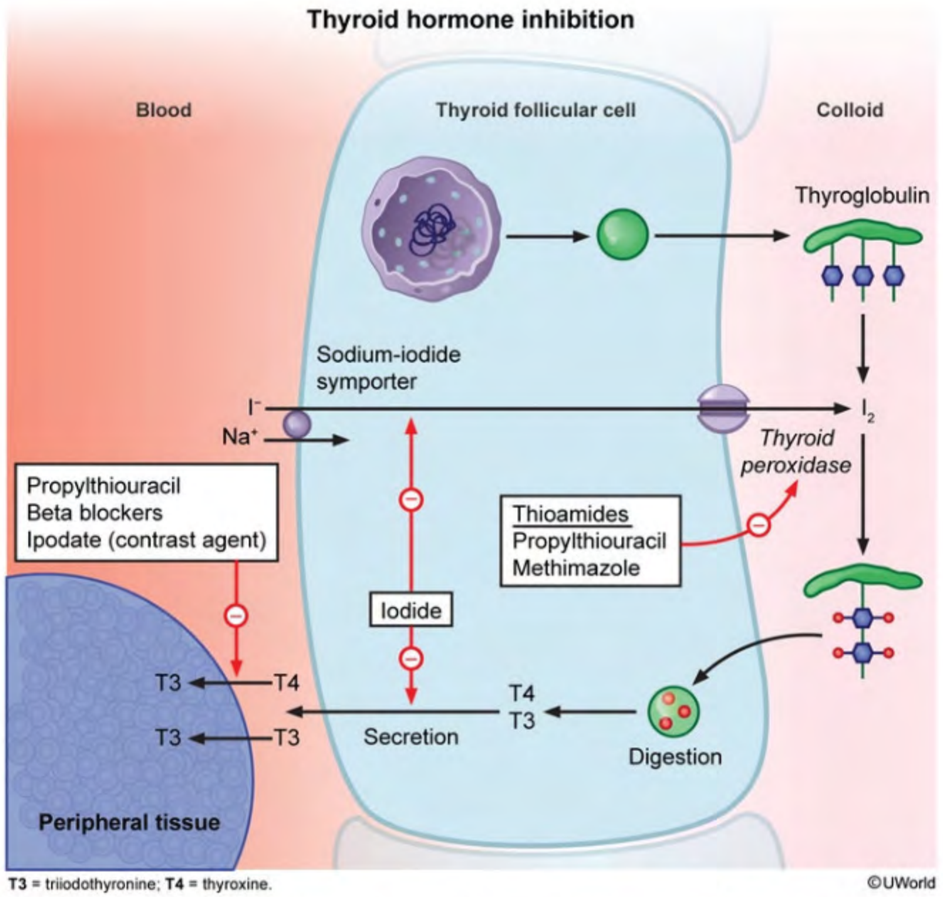
(Choic
additic

(Choic
adrene
inhibit

(Choic
produc

Educa
Conge
of mat
maternal hyperthyroidism.

Exhibit Display



Zoom In Zoom Out Reset New | Existing My Notebook

https://t.me/USMLEWorldStep1

FT4 = free thyroxine.

This n
The m
decrea

One c
medic
Grave
thyroic

Propyl
increa
norma
propyl
TSH, 1
the ne

(Choi
additic

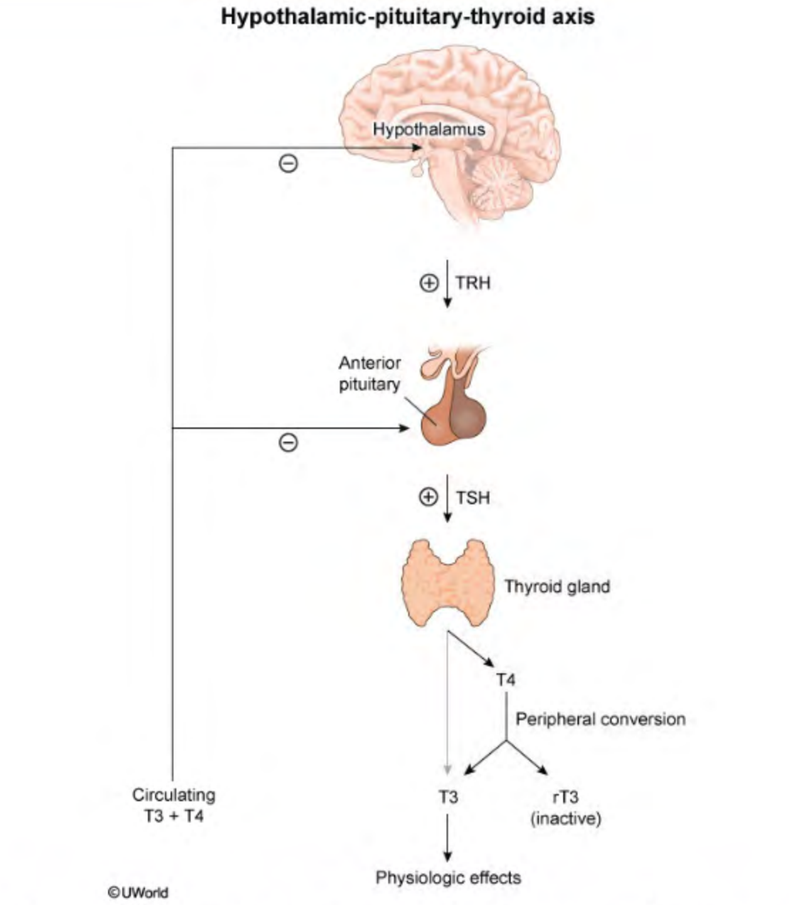
(Choi
adrene
inhibit

(Choi
produc

Educa
Conge
of mat
maternal hyperthyroidism.

References

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

A 34-year-old man develops excessive thirst and frequent urination while being hospitalized for multiple injuries following a motorcycle collision. His urinary osmolality after 4 hours of water restriction is 250 mOsm/L and increases to 700 mOsm/L after administration of antidiuretic hormone. The patient is started on an appropriate medication, and his symptoms promptly resolve. Over the next 2 years, multiple attempts are made to wean the patient off the medication, but his symptoms would always return, necessitating the resumption of treatment. The permanence of this patient's condition is best explained by traumatic damage to which of the following structures?

- A. Anterior pituitary
- B. Hypothalamic nuclei
- C. Kidneys
- D. Posterior pituitary
- E. Thalamic nuclei

Submit

https://t.me/USMLEWorldStep1

A 34-year-old man develops excessive thirst and frequent urination while being hospitalized for multiple injuries following a motorcycle collision. His urinary osmolality after 4 hours of water restriction is 250 mOsm/L and increases to 700 mOsm/L after administration of antidiuretic hormone. The patient is started on an appropriate medication, and his symptoms promptly resolve. Over the next 2 years, multiple attempts are made to wean the patient off the medication, but his symptoms would always return, necessitating the resumption of treatment. The permanence of this patient's condition is best explained by traumatic damage to which of the following structures?

- A. Anterior pituitary (5%)
- ✓ B. Hypothalamic nuclei (46%)
- C. Kidneys (2%)
- D. Posterior pituitary (45%)
- E. Thalamic nuclei (0%)

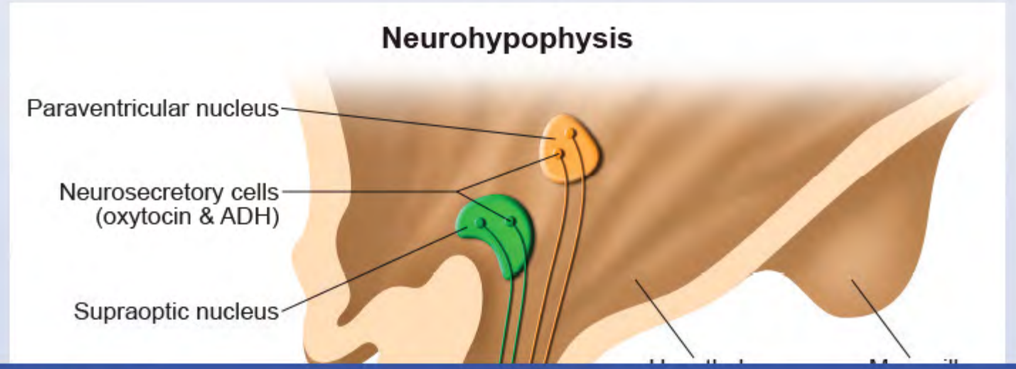
Correct

46% Answered correctly

03 secs Time Spent

2023 Version

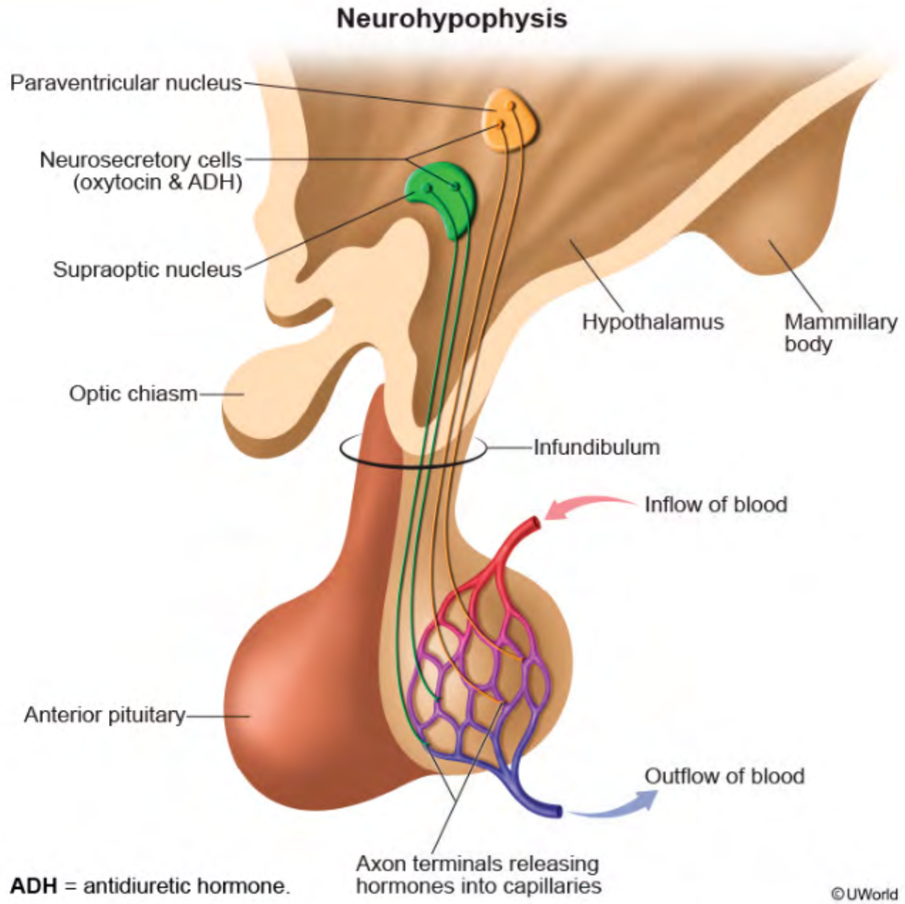
Explanation



https://t.me/USMLEWorldStep1

A 34-year-old man develops excessive thirst and frequent urination while being hospitalized for multiple injuries
followi
increa
medic
patien
perma

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Supraoptic nucleus

https://t.me/USMLEWorldStep1

This patient has **diabetes insipidus** (DI), a condition that results in the production of large volumes of very dilute urine due to impaired antidiuretic hormone (ADH) activity. DI can be due to deficient ADH production in the brain **(central)** or resistance to ADH in the kidneys (nephrogenic). Injection of exogenous ADH can help distinguish between central and nephrogenic DI: **ADH administration** substantially **increases urine osmolality** in patients with central DI, whereas patients with nephrogenic DI typically have a more limited increase in urine osmolality (<300 mOsm/L increase).

ADH is synthesized by magnocellular neurosecretory cells in the paraventricular and supraoptic nuclei of the hypothalamus. These neurons project axons to the posterior pituitary where axon terminals store large quantities of ADH for later release into the circulation. Injury to the hypothalamus or posterior pituitary (eg, head trauma, transsphenoidal neurosurgery, suprasellar masses) can result in central DI. Damage to the more distal portions of the hypothalamic-hypophyseal tract (ie, below the infundibulum) typically causes transient DI because the cell bodies of the magnocellular neurons remain intact. However, **hypothalamic injury** results in death of the magnocellular neurons, causing **permanent central DI**.

(Choice A) The anterior pituitary produces ACTH, TSH, gonadotrophic hormones, prolactin, and growth hormone. Hormone secretion from the anterior pituitary is regulated by substances released from the median eminence into the hypothalamic-hypophyseal portal vessels.

(Choice C) Although head trauma is a frequent cause of central DI, traumatic damage to the kidneys does not result in nephrogenic DI. Furthermore, this patient's large increase in urine concentration following ADH administration is more suggestive of central DI.

(Choice D) Isolated posterior pituitary damage most often causes transient central DI because the cell bodies of the magnocellular neurons remain intact and can undergo axonal regeneration to allow adequate ADH release into the circulation.

(Choice E) Thalamic nuclei are involved in relaying sensory and motor signals to the cerebral cortex and in regulating alertness and consciousness.

Educational objective:
Injury to the hypothalamus or posterior pituitary (eg, head trauma, transsphenoidal neurosurgery, suprasellar masses) can result in central diabetes insipidus (DI). Damage to the posterior pituitary gland typically causes

https://t.me/USMLEWorldStep1

between central and nephrogenic DI. **ADH administration** substantially **increases urine osmolality** in patients with central DI, whereas patients with nephrogenic DI typically have a more limited increase in urine osmolality (<300 mOsm/L increase).

ADH is synthesized by magnocellular neurosecretory cells in the paraventricular and supraoptic nuclei of the hypothalamus. These neurons project axons to the posterior pituitary where axon terminals store large quantities of ADH for later release into the circulation. Injury to the hypothalamus or posterior pituitary (eg, head trauma, transsphenoidal neurosurgery, suprasellar masses) can result in central DI. Damage to the more distal portions of the hypothalamic-hypophyseal tract (ie, below the infundibulum) typically causes transient DI because the cell bodies of the magnocellular neurons remain intact. However, **hypothalamic injury** results in death of the magnocellular neurons, causing **permanent central DI**.

(Choice A) The anterior pituitary produces ACTH, TSH, gonadotrophic hormones, prolactin, and growth hormone. Hormone secretion from the anterior pituitary is regulated by substances released from the median eminence into the hypothalamic-hypophyseal portal vessels.

(Choice C) Although head trauma is a frequent cause of central DI, traumatic damage to the kidneys does not result in nephrogenic DI. Furthermore, this patient's large increase in urine concentration following ADH administration is more suggestive of central DI.

(Choice D) Isolated posterior pituitary damage most often causes transient central DI because the cell bodies of the magnocellular neurons remain intact and can undergo axonal regeneration to allow adequate ADH release into the circulation.

(Choice E) Thalamic nuclei are involved in relaying sensory and motor signals to the cerebral cortex and in regulating alertness and consciousness.

Educational objective:
Injury to the hypothalamus or posterior pituitary (eg, head trauma, transsphenoidal neurosurgery, suprasellar masses) can result in central diabetes insipidus (DI). Damage to the posterior pituitary gland typically causes transient DI, whereas damage to the hypothalamic nuclei often causes permanent DI.

References

- Diabetes Insipidus after Traumatic Brain Injury

https://t.me/USMLEWorldStep1

A 47-year-old woman has a tumor that is causing symptoms of excessive hormone production. Surgical resection of the lesion is performed with no operative complications, and the neoplastic tissue is subjected to detailed pathologic studies. Electron microscopy reveals the tumor cells have highly developed, smooth endoplasmic reticulum. Which of the following is a possible direct effect of the substance secreted by these cells?

- A. Increase in water reabsorption in the renal collecting ducts
- B. Induction of hypoglycemia with increased cellular glucose uptake
- C. Promotion of male-pattern hair growth and virilization
- D. Stimulation of acid secretion from the gastric parietal cells
- E. Stimulation of milk production by the mammary tissue

Submit

https://t.me/USMLEWorldStep1

A 47-year-old woman has a tumor that is causing symptoms of excessive hormone production. Surgical resection of the lesion is performed with no operative complications, and the neoplastic tissue is subjected to detailed pathologic studies. Electron microscopy reveals the tumor cells have highly developed, smooth endoplasmic reticulum. Which of the following is a possible direct effect of the substance secreted by these cells?

- A. Increase in water reabsorption in the renal collecting ducts (8%)
- ✗ B. Induction of hypoglycemia with increased cellular glucose uptake (10%)
- ✓ C. Promotion of male-pattern hair growth and virilization (63%)
- D. Stimulation of acid secretion from the gastric parietal cells (3%)
- E. Stimulation of milk production by the mammary tissue (12%)

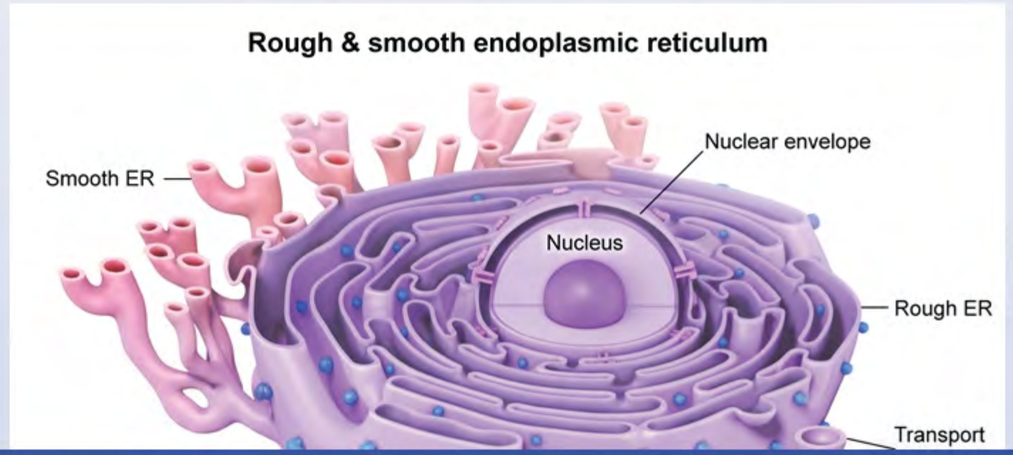
Incorrect
Correct answer
C

63%
Answered correctly

03 secs
Time Spent

2023
Version

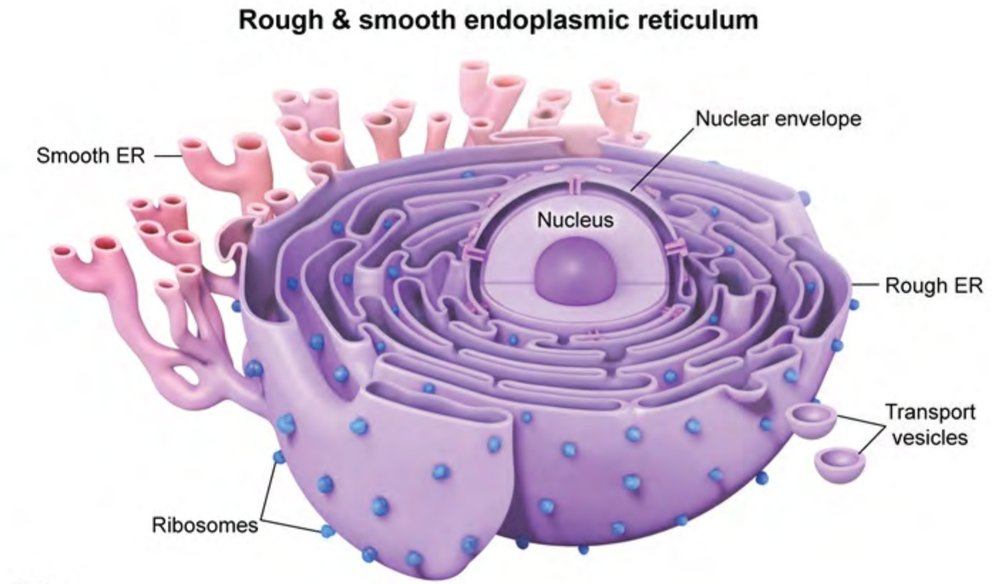
Explanation



https://t.me/USMLEWorldStep1

A 47-year-old woman has a tumor that is causing symptoms of excessive hormone production. Surgical resection of the
pathol
reticul

Exhibit Display



Zoom In Zoom Out Reset New | Existing My Notebook

Transport

https://t.me/USMLEWorldStep1



The endoplasmic reticulum (ER) is an interconnected, membrane-bound network found in almost all eukaryotic cells. It is highly metabolically active and plays a significant role in the synthesis and modification of cellular components. The ER is recognizable on electron microscopy as a flattened tubular or laminar structure near or adjacent to the nucleus.

The **smooth endoplasmic reticulum** (SER) is involved in the synthesis and processing of hydrophobic compounds, including lipids, phospholipids, and cholesterol derivatives (eg, **steroid hormones**). Cholesterol is initially converted to pregnenolone in the mitochondria and then transferred to the SER, where the remaining steps of steroidogenesis occur. The SER contains the enzymes (eg, 21-hydroxylase) required for steroid and phospholipid biosynthesis. Steroid-producing cells (in the adrenals, gonads, and liver) characteristically contain a well-developed SER. This patient is likely experiencing **virilization** due to an **androgen-secreting** ovarian or adrenal **tumor**. Paraneoplastic syndromes can also occur due to overproduction of other sex steroids, cortisol (ie, Cushing syndrome), or aldosterone.

By contrast, the rough endoplasmic reticulum (RER) is characterized by numerous ribosomes on the outer membrane. The RER plays an important role in the synthesis and modification of targeted proteins, including secretable polypeptide hormones. Some of the clinically significant syndromes due to overproduction of **peptide hormones** by the RER include:

- Syndrome of inappropriate antidiuretic hormone (characterized by increased water reabsorption in the renal collecting ducts), often abbreviated SIADH, due to overproduction of vasopressin **(Choice A)**
- Hypoglycemia due to overproduction of insulin by certain pancreatic neuroendocrine tumors (insulinomas) **(Choice B)**
- Zollinger-Ellison syndrome (gastric acid hypersecretion and recurrent peptic ulcer) due to excess secretion of gastrin from pancreatic or small intestine gastrinomas **(Choice D)**
- Galactorrhea (pathologic mammary milk production) due to a prolactin-secreting lactotroph pituitary adenoma **(Choice E)**

https://t.me/USMLEWorldStep1

The **smooth endoplasmic reticulum** (SER) is involved in the synthesis and processing of hydrophobic compounds, including lipids, phospholipids, and cholesterol derivatives (eg, **steroid hormones**). Cholesterol is initially converted to pregnenolone in the mitochondria and then transferred to the SER, where the remaining steps of steroidogenesis occur. The SER contains the enzymes (eg, 21-hydroxylase) required for steroid and phospholipid biosynthesis. Steroid-producing cells (in the adrenals, gonads, and liver) characteristically contain a well-developed SER. This patient is likely experiencing **virilization** due to an **androgen-secreting** ovarian or adrenal **tumor**. Paraneoplastic syndromes can also occur due to overproduction of other sex steroids, cortisol (ie, Cushing syndrome), or aldosterone.

By contrast, the rough endoplasmic reticulum (RER) is characterized by numerous ribosomes on the outer membrane. The RER plays an important role in the synthesis and modification of targeted proteins, including secretable polypeptide hormones. Some of the clinically significant syndromes due to overproduction of **peptide hormones** by the RER include:

- Syndrome of inappropriate antidiuretic hormone (characterized by increased water reabsorption in the renal collecting ducts), often abbreviated SIADH, due to overproduction of vasopressin **(Choice A)**
- Hypoglycemia due to overproduction of insulin by certain pancreatic neuroendocrine tumors (insulinomas) **(Choice B)**
- Zollinger-Ellison syndrome (gastric acid hypersecretion and recurrent peptic ulcer) due to excess secretion of gastrin from pancreatic or small intestine gastrinomas **(Choice D)**
- Galactorrhea (pathologic mammary milk production) due to a prolactin-secreting lactotroph pituitary adenoma **(Choice E)**

Educational objective:
The initial step in the synthesis of steroid hormones is the conversion of cholesterol to pregnenolone in the mitochondria. The remainder of steroidogenesis occurs in the smooth endoplasmic reticulum. Steroid-producing cells contain a well-developed smooth endoplasmic reticulum.

References

- The endoplasmic reticulum: structure, function and response to cellular signaling.

https://t.me/USMLEWorldStep1

A 24-year-old woman, gravida 1 para 1, comes to the office for postpartum follow-up 2 weeks after a term vaginal delivery. Her baby is doing well, but she is concerned because she has not yet lactated. The patient knew she would lose weight and be tired after the baby was born, but she feels excessive fatigue and has had significant weight loss. She also has nausea, loss of appetite, and postural dizziness. The patient has no headaches, visual problems, cold intolerance, constipation, or polyuria. On examination, she appears fatigued and has mild pallor. Laboratory tests are drawn the next morning at 8:00 AM, with the following results:

Hemoglobin	9.6 g/dL
Sodium	130 mEq/L
Cortisol, serum	4 µg/dL
Free T_4	1.0 ng/dL
TSH	0.2 µU/mL

Which of the following pathologic processes is most likely responsible for this patient's symptoms?

- A. Glandular hemorrhage
- B. Inflammation
- C. Ischemic necrosis
- D. Malignant infiltration
- E. Non-malignant infiltration

Submit

https://t.me/USMLEWorldStep1

A 24-year-old woman, gravida 1 para 1, comes to the office for postpartum follow-up 2 weeks after a term vaginal delivery. Her baby is doing well, but she is concerned because she has not yet lactated. The patient knew she would lose weight and be tired after the baby was born, but she feels excessive fatigue and has had significant weight loss. She also has nausea, loss of appetite, and postural dizziness. The patient has no headaches, visual problems, cold intolerance, constipation, or polyuria. On examination, she appears fatigued and has mild pallor. Laboratory tests are drawn the next morning at 8:00 AM, with the following results:

Hemoglobin	9.6 g/dL
Sodium	130 mEq/L
Cortisol, serum	4 µg/dL
Free T_4	1.0 ng/dL
TSH	0.2 µU/mL

Which of the following pathologic processes is most likely responsible for this patient's symptoms?

- ✗ A. Glandular hemorrhage (21%)
- B. Inflammation (1%)
- ✓ C. Ischemic necrosis (72%)
- D. Malignant infiltration (1%)
- E. Non-malignant infiltration (2%)

Incorrect
Correct answer
C

72%
Answered correctly

04 secs
Time Spent

2023
Version

https://t.me/USMLEWorldStep1

Clinical features of hypopituitarism	
Etiology	• Pituitary causes ◦ Primary (eg, adenoma) or metastatic mass ◦ Infiltration (eg, hemochromatosis, lymphocytic hypophysitis) ◦ Hemorrhage (pituitary apoplexy) or infarction (Sheehan syndrome) • Hypothalamic causes ◦ Mass lesions ◦ Radiation therapy ◦ Infiltration (sarcoidosis) ◦ Trauma to skull base ◦ Infections (tuberculosis meningitis)
Clinical presentation	• ACTH deficiency (secondary adrenal insufficiency) ◦ Postural hypotension, tachycardia, fatigue, weight loss, hypoglycemia, eosinophilia • Hypothyroidism (central) ◦ Fatigue, cold intolerance, constipation, dry skin, bradycardia, slowed deep-tendon reflexes • Gonadotropins ◦ Women: amenorrhea, infertility ◦ Men: infertility, loss of libido

This patient has signs of **panhypopituitarism** with failure of lactation, central hypothyroidism, and adrenal insufficiency. In the setting of a recent delivery, this most likely represents **ischemic necrosis** of the **pituitary gland** (Sheehan syndrome). During pregnancy, the pituitary enlarges due to estrogen-induced hyperplasia of the lactotrophs. However, the blood supply to the pituitary does not increase proportionally. As a result, the enlarged pituitary is vulnerable to ischemia in case of systemic hypotension due to **peripartum hemorrhage** (which this patient likely experienced given her low hemoglobin).

https://t.me/USMLEWorldStep1

	◦ Women: amenorrhea, infertility ◦ Men: infertility, loss of libido

This patient has signs of **panhypopituitarism** with failure of lactation, central hypothyroidism, and adrenal insufficiency. In the setting of a recent delivery, this most likely represents **ischemic necrosis** of the **pituitary gland** (Sheehan syndrome). During pregnancy, the pituitary enlarges due to estrogen-induced hyperplasia of the lactotrophs. However, the blood supply to the pituitary does not increase proportionally. As a result, the enlarged pituitary is vulnerable to ischemia in case of systemic hypotension due to **peripartum hemorrhage** (which this patient likely experienced given her low hemoglobin).

The most common manifestation of Sheehan syndrome is failure of lactation due to prolactin deficiency. It also commonly causes hypocortisolism and hypothyroidism. Manifestations of thyroid deficiency may take a few weeks to develop due to the long circulating half-life of thyroxine (5-7 days) and peripheral conversion of thyroxine (T4) to T3. Cortisol deficiency manifests rapidly, however, with nausea, postural hypotension, fatigue, and weight loss.

(Choice A) Pituitary apoplexy is due to sudden hemorrhage into the pituitary, usually in the setting of a preexisting pituitary adenoma. It usually presents with acute severe headache, ophthalmoplegia, and altered sensorium.

(Choice B) Lymphocytic hypophysitis is the most common inflammatory condition of the pituitary and typically occurs during late pregnancy or the early postpartum period. In contrast to Sheehan syndrome, the presentation is acute with severe headaches and visual field defects.

(Choice D) Primary pituitary cancer is extremely rare, although the pituitary is prone to metastases due to its rich vascular supply. These patients typically present with tumor mass effects (eg, headache, bitemporal hemianopsia).

(Choice E) Non-malignant infiltrative lesions such as sarcoidosis and histiocytosis X mainly involve the suprasellar region, where they compress the hypothalamus and pituitary stalk. This disrupts the normal hypothalamic dopaminergic suppression of prolactin secretion, leading to increased prolactin levels and possible galactorrhea. Central diabetes insipidus may also be seen with resulting hypernatremia.

Educational objective:
High estrogen levels during pregnancy cause enlargement of the pituitary gland without a proportional increase in blood supply. Peripartum hypotension can cause ischemic necrosis of the pituitary leading to panhypopituitarism

https://t.me/USMLEWorldStep1

insufficiency. In the setting of a recent delivery, this most likely represents **ischemic necrosis** of the **pituitary gland** (Sheehan syndrome). During pregnancy, the pituitary enlarges due to estrogen-induced hyperplasia of the lactotrophs. However, the blood supply to the pituitary does not increase proportionally. As a result, the enlarged pituitary is vulnerable to ischemia in case of systemic hypotension due to **peripartum hemorrhage** (which this patient likely experienced given her low hemoglobin).

The most common manifestation of Sheehan syndrome is failure of lactation due to prolactin deficiency. It also commonly causes hypocortisolism and hypothyroidism. Manifestations of thyroid deficiency may take a few weeks to develop due to the long circulating half-life of thyroxine (5-7 days) and peripheral conversion of thyroxine (T4) to T3. Cortisol deficiency manifests rapidly, however, with nausea, postural hypotension, fatigue, and weight loss.

(Choice A) Pituitary apoplexy is due to sudden hemorrhage into the pituitary, usually in the setting of a preexisting pituitary adenoma. It usually presents with acute severe headache, ophthalmoplegia, and altered sensorium.

(Choice B) Lymphocytic hypophysitis is the most common inflammatory condition of the pituitary and typically occurs during late pregnancy or the early postpartum period. In contrast to Sheehan syndrome, the presentation is acute with severe headaches and visual field defects.

(Choice D) Primary pituitary cancer is extremely rare, although the pituitary is prone to metastases due to its rich vascular supply. These patients typically present with tumor mass effects (eg, headache, bitemporal hemianopsia).

(Choice E) Non-malignant infiltrative lesions such as sarcoidosis and histiocytosis X mainly involve the suprasellar region, where they compress the hypothalamus and pituitary stalk. This disrupts the normal hypothalamic dopaminergic suppression of prolactin secretion, leading to increased prolactin levels and possible galactorrhea. Central diabetes insipidus may also be seen with resulting hypernatremia.

Educational objective:
High estrogen levels during pregnancy cause enlargement of the pituitary gland without a proportional increase in blood supply. Peripartum hypotension can cause ischemic necrosis of the pituitary leading to panhypopituitarism (Sheehan syndrome). Patients commonly develop failure of lactation due to deficiency of prolactin.

References

- Sheehan's syndrome.

https://t.me/USMLEWorldStep1

A 30-year-old woman is evaluated for a 3-month history of progressive fatigue, decreased appetite, and 10-lb (4.5-kg) weight loss. The patient has type 1 diabetes mellitus and has noticed decreased insulin requirements over this time. She has no other medical conditions and does not use tobacco, alcohol, or illicit drugs. Physical examination shows a generalized increase in pigmentation of the skin, especially involving the palmar creases. Measurement of serum cortisol before and after administration of exogenous adrenocorticotropic hormone (ACTH) shows no difference in the levels. Which of the following changes in serum laboratory values is most likely present in this patient?

	Sodium	Potassium	Chloride	Bicarbonate
○ A.	Normal	↓	↓	↑
○ B.	↓	↑	↑	↓
○ C.	↓	↓	↓	↑
○ D.	Normal	↑	Normal	Normal
○ E.	Normal	↓	↑	↓

Submit

https://t.me/USMLEWorldStep1

A 30-year-old woman is evaluated for a 3-month history of progressive fatigue, decreased appetite, and 10-lb (4.5-kg) weight loss. The patient has type 1 diabetes mellitus and has noticed decreased insulin requirements over this time. She has no other medical conditions and does not use tobacco, alcohol, or illicit drugs. Physical examination shows a generalized increase in pigmentation of the skin, especially involving the palmar creases. Measurement of serum cortisol before and after administration of exogenous adrenocorticotropic hormone (ACTH) shows no difference in the levels. Which of the following changes in serum laboratory values is most likely present in this patient?

	Sodium	Potassium	Chloride	Bicarbonate	
A.	Normal	↓	↓	↑	(16%)
✓ B.	↓	↑	↑	↓	(51%)
✗ C.	↓	↓	↓	↑	(7%)
D.	Normal	↑	Normal	Normal	(13%)
E.	Normal	↓	↑	↓	(10%)

Incorrect
Correct answer
B

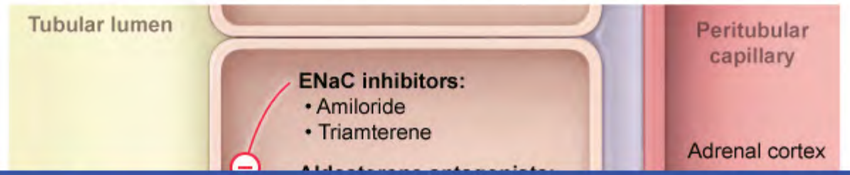
51%
Answered correctly

06 secs
Time Spent

2023
Version

Explanation

Action of aldosterone in the collecting duct of the nephron

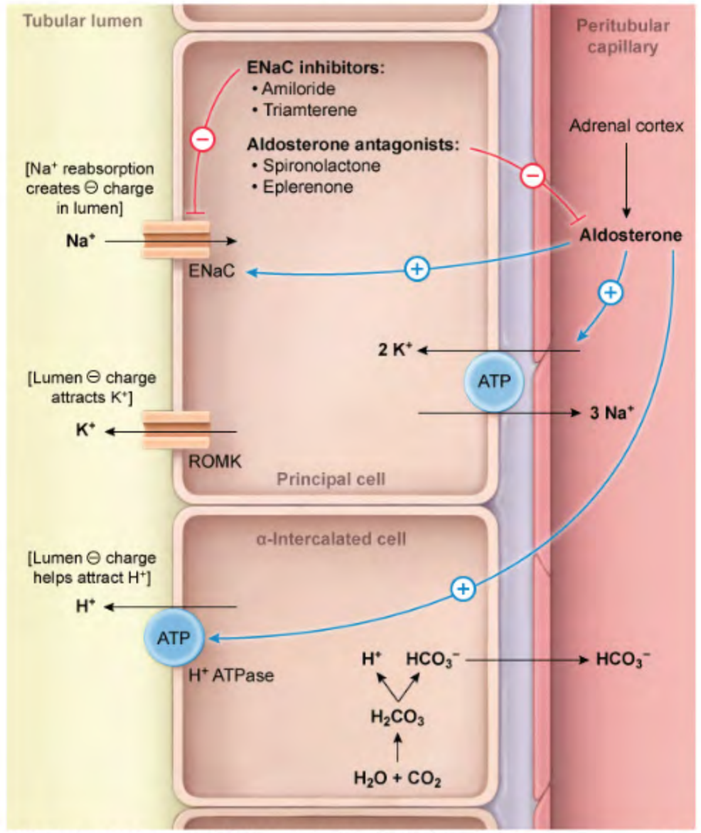


https://t.me/USMLEWorldStep1

A 30-year-old woman is evaluated for a 3-month history of progressive fatigue, decreased appetite, and 10-lb (4.5-kg) we
time.
exami
Measu
shows
in this

Exhibit Display

Action of aldosterone in the collecting duct of the nephron



ENaC = epithelial sodium channel; **ROMK** = renal outer medullary potassium channel. ©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1



ENaC = epithelial sodium channel; **ROMK** = renal outer medullary potassium channel. ©UWorld

This patient's fatigue and weight loss are likely due to **primary adrenal insufficiency** (Addison disease). Type 1 diabetes mellitus is caused by autoimmune destruction of pancreatic beta cells and is associated with an increased risk of other autoimmune endocrinopathies. Autoimmune adrenalitis is the most common cause of primary adrenal insufficiency and results from autoantibodies against all 3 zones of the adrenal cortex. Because the main defect is in the adrenal gland, **exogenous ACTH** administration **does not increase cortisol** levels. Decreased negative feedback of cortisol on the pituitary gland increases release of ACTH and melanocyte-stimulating hormone, resulting in **hyperpigmentation**. Patients with diabetes often have reduced insulin requirements due to decreased appetite, weight loss, and increased insulin sensitivity (glucocorticoids decrease insulin sensitivity).

Hypoaldosteronism in primary adrenal insufficiency leads to decreased Na^+ reabsorption and decreased urinary excretion of K^+ and H^+. Decreased H^+ excretion causes a nonanion gap metabolic acidosis with low plasma HCO_3^-. This leads to compensatory Cl^- retention to maintain electrical neutrality of the extracellular fluid. The hypotension induced by lack of aldosterone stimulates vasopressin release, increasing free water reabsorption and further exacerbating hyponatremia. As a result, patients with primary adrenal insufficiency present with **hyponatremia**, **hyperkalemia**, hyperchloremia, and **nonanion gap metabolic acidosis**.

(Choice A) Mineralocorticoid excess (ie, primary hyperaldosteronism) leads to Na^+ retention, urinary loss of K^+ and H^+, and metabolic alkalosis (ie, increased plasma HCO_3^-). However, significant hypernatremia is avoided due to aldosterone escape.

(Choice C) Thiazide diuretics block Na^+/Cl^- reabsorption in the distal tubule. This allows more Na^+ to reach the collecting tubule, enhancing K^+ and H^+ excretion. Findings include hyponatremia, hypokalemia, and metabolic alkalosis.

(Choice D) Isolated hyperkalemia is usually due to excess dietary potassium intake or cell lysis (eg, hemolysis, rhabdomyolysis). Hyperkalemia can also be caused by decreased shift of K^+ into the cells due to insulin deficiency or occasionally by beta 2 antagonists (eg, metoprolol).

(Choice E) Normal serum sodium in the setting of hypokalemia and hyperchloremic metabolic acidosis suggests

https://t.me/USMLEWorldStep1

in the adrenal gland, **exogenous ACTH** administration **does not increase cortisol** levels. Decreased negative feedback of cortisol on the pituitary gland increases release of ACTH and melanocyte-stimulating hormone, resulting in **hyperpigmentation**. Patients with diabetes often have reduced insulin requirements due to decreased appetite, weight loss, and increased insulin sensitivity (glucocorticoids decrease insulin sensitivity).

Hypoaldosteronism in primary adrenal insufficiency leads to decreased Na^+ reabsorption and decreased urinary excretion of K^+ and H^+. Decreased H^+ excretion causes a nonanion gap metabolic acidosis with low plasma HCO_3^-. This leads to compensatory Cl^- retention to maintain electrical neutrality of the extracellular fluid. The hypotension induced by lack of aldosterone stimulates vasopressin release, increasing free water reabsorption and further exacerbating hyponatremia. As a result, patients with primary adrenal insufficiency present with **hyponatremia**, **hyperkalemia**, hyperchloremia, and **nonanion gap metabolic acidosis**.

(Choice A) Mineralocorticoid excess (ie, primary hyperaldosteronism) leads to Na^+ retention, urinary loss of K^+ and H^+, and metabolic alkalosis (ie, increased plasma HCO_3^-). However, significant hypernatremia is avoided due to aldosterone escape.

(Choice C) Thiazide diuretics block Na^+/Cl^- reabsorption in the distal tubule. This allows more Na^+ to reach the collecting tubule, enhancing K^+ and H^+ excretion. Findings include hyponatremia, hypokalemia, and metabolic alkalosis.

(Choice D) Isolated hyperkalemia is usually due to excess dietary potassium intake or cell lysis (eg, hemolysis, rhabdomyolysis). Hyperkalemia can also be caused by decreased shift of K^+ into the cells due to insulin deficiency or occasionally by beta 2 antagonists (eg, metoprolol).

(Choice E) Normal serum sodium in the setting of hypokalemia and hyperchloremic metabolic acidosis suggests distal hypokalemic or proximal renal tubular acidosis.

Educational objective:
Patients with type 1 diabetes mellitus are at increased risk for other autoimmune endocrinopathies, including primary adrenal insufficiency (Addison disease). Electrolyte abnormalities in primary adrenal insufficiency include hyponatremia, hyperkalemia, hyperchloremia, and nonanion gap metabolic acidosis.

References

https://t.me/USMLEWorldStep1

in the adrenal gland, **exogenous ACTH** administration **does not increase cortisol** levels. Decreased negative feedback of cortisol on the pituitary gland increases release of ACTH and melanocyte-stimulating hormone

resulti

appeti

Hypoa

excret

This le

induce

exacer

hyper

(Choi

H^+, an

aldost

(Choi

collect

alkalos

(Choi

rhabd

or occ

(Choi

distal

Educa

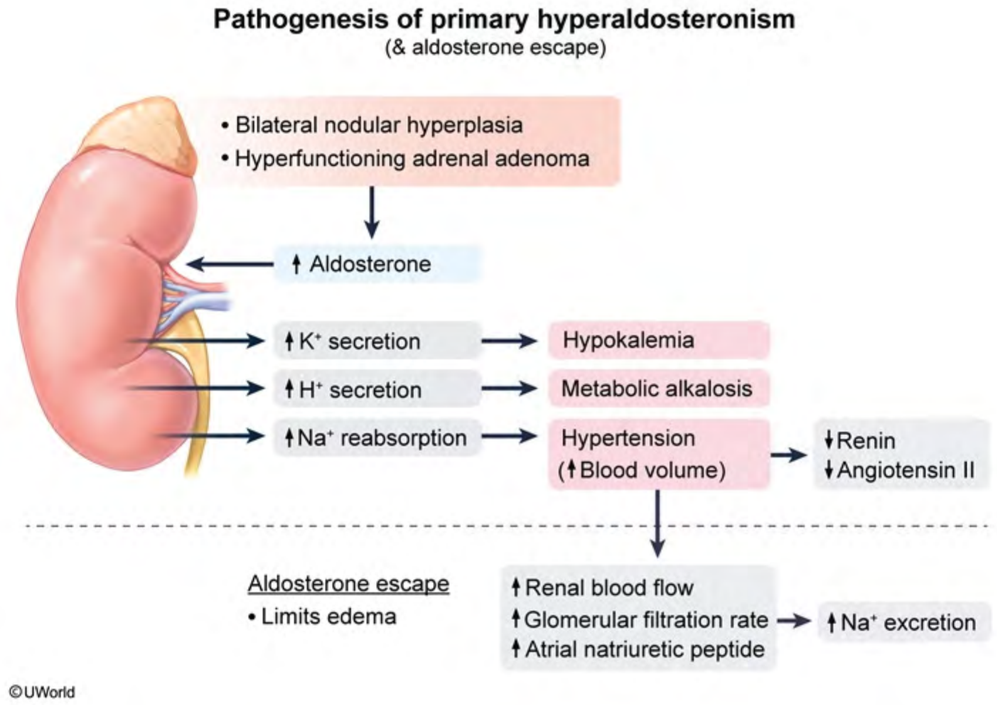
Patien

primar

hypon

References

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

A researcher is investigating factors affecting adrenal hormone synthesis and release. An intact adrenal gland is obtained from a donor cadaver, and a histologic section of the gland is shown below. Cells from a specific part of the gland, indicated by the arrow, are extracted for further analysis.

These cells are most likely to be directly activated by which of the following substances?

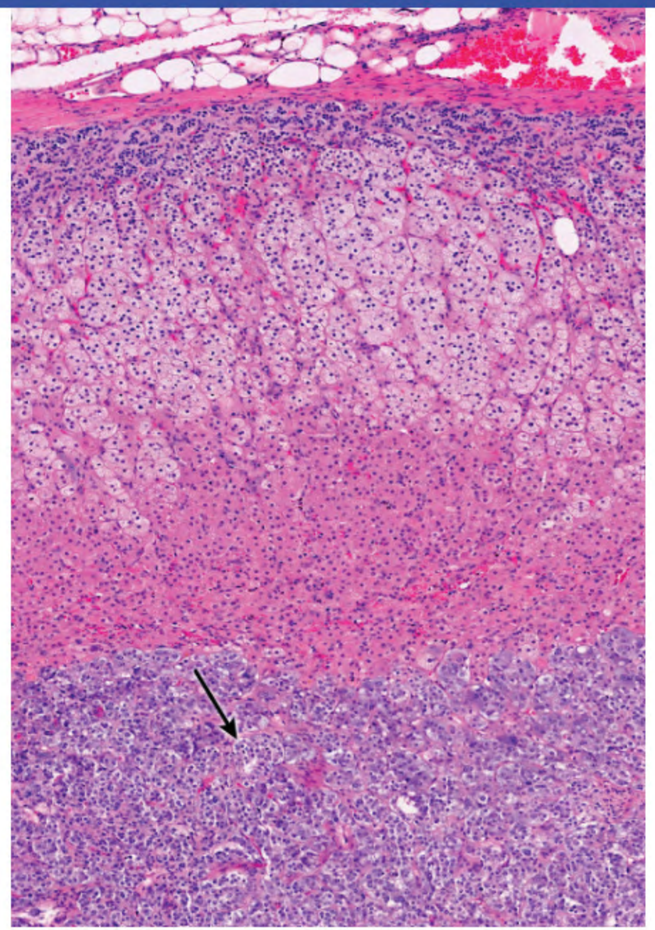
- A. Acetylcholine
- B. ACTH
- C. Angiotensin II
- D. Epinephrine
- E. Norepinephrine

Submit

https://t.me/USMLEWorldStep1

A researcher is investigating factors affecting adrenal hormone synthesis and release. An intact adrenal gland is obtain
the gla

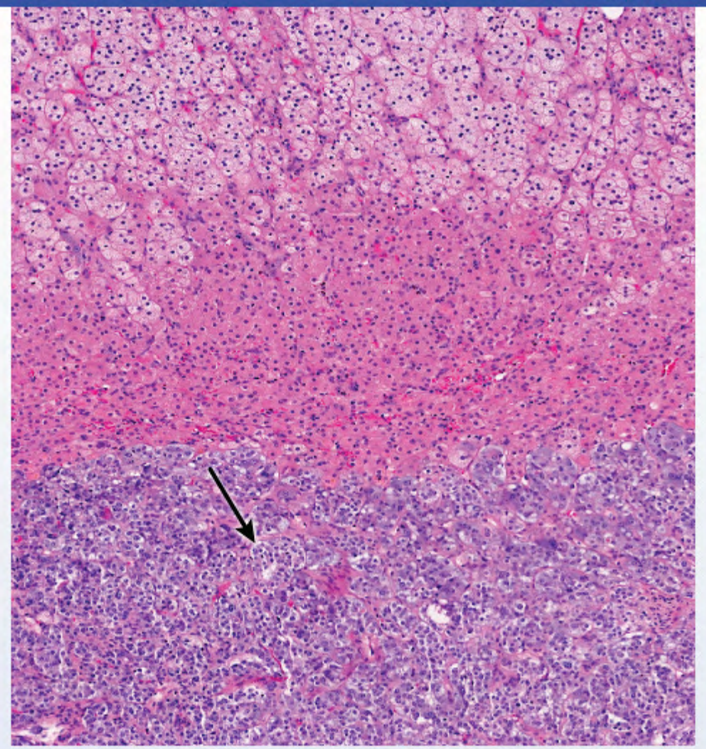
Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

These cells are most likely to be directly activated by which of the following substances?

https://t.me/USMLEWorldStep1

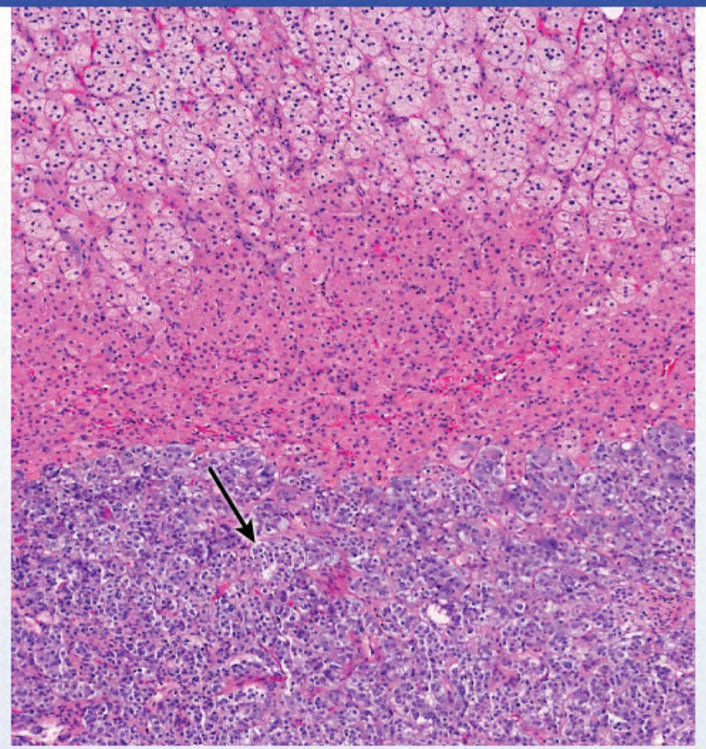


These cells are most likely to be directly activated by which of the following substances?

- A. Acetylcholine
- B. ACTH
- C. Angiotensin II
- D. Epinephrine
- E. Norepinephrine

Submit

https://t.me/USMLEWorldStep1



These cells are most likely to be directly activated by which of the following substances?

- ✓ A. Acetylcholine (42%)
- B. ACTH (28%)
- C. Angiotensin II (10%)
- ✗ D. Epinephrine (10%)
- E. Norepinephrine (8%)

Incorrect
Correct answer
A

42%
Answered correctly

24 secs
Time Spent

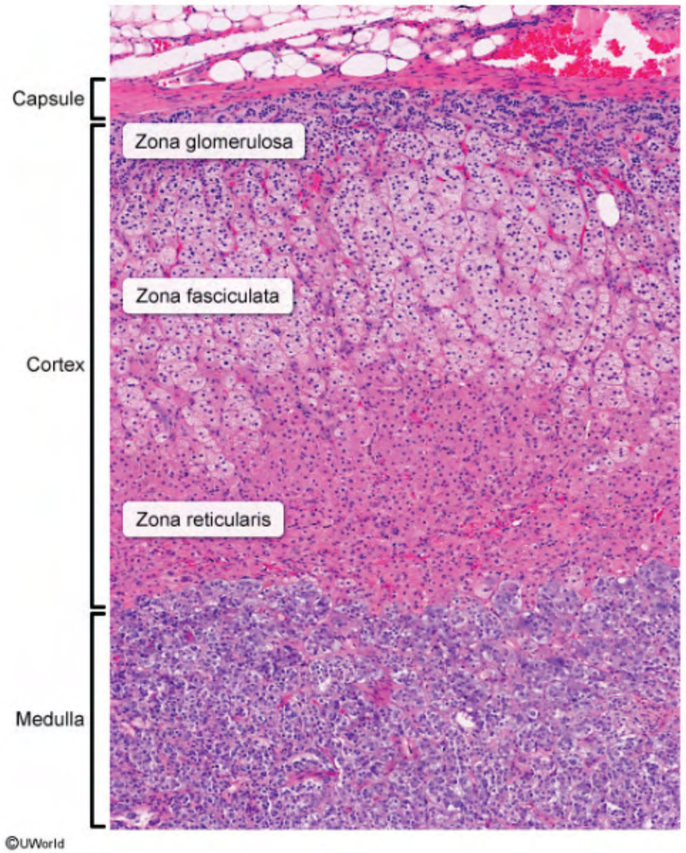
2023
Version

https://t.me/USMLEWorldStep1

D. Epinephrine (10%)

Exhibit Display

Normal adrenal gland



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

The adrenal gland is made up of an outer cortex (divided into 3 zones) and an inner medulla:

1. The zona glomerulosa is the outermost zone of the cortex and is composed of cells arranged in rounded or arched clusters (*glomus* is Latin for ball) that secrete mineralocorticoid hormones (primarily aldosterone).
2. The zona fasciculata is the middle zone and contains foamy-appearing cells in columns (*fascis* is Latin for bundle or stack) that secrete glucocorticoid hormones (primarily cortisol).
3. The zona reticularis is the inner zone of the cortex and contains cells in anastomosing cords (*rete* is Latin for net) that secrete androgens.
4. The **adrenal medulla** is sharply demarcated from the cortex and is composed of chromaffin cells with a deeply basophilic cytoplasm.

Chromaffin cells are modified neuroendocrine cells derived from the neural crest. They are **stimulated by acetylcholine** released by sympathetic preganglionic neurons and **secrete catecholamines** (80% epinephrine, 20% norepinephrine) directly into the bloodstream to amplify sympathetic nervous system activity.

(Choice B) ACTH stimulates secretion of glucocorticoid hormones from the zona fasciculata. Cortisol produced in response to ACTH increases activity of the adrenal medullary enzyme phenylethanolamine N-methyltransferase, which catalyzes the conversion of norepinephrine to epinephrine. ACTH therefore indirectly upregulates medullary epinephrine production, but does not directly control it.

(Choice C) Aldosterone secretion from the zona glomerulosa is primarily regulated by angiotensin II and extracellular potassium levels.

(Choice D) Epinephrine released by the adrenal medulla acts on adrenergic receptors in the heart, lungs, liver, and skeletal muscle to increase sympathetic tone and mediate the acute stress response.

(Choice E) Most sympathetic *postganglionic* neurons release norepinephrine to activate adrenergic receptors on the target tissues. However, the *preganglionic* fibers innervating the adrenal medulla (and postganglionic sympathetic neurons innervating eccrine sweat glands) release acetylcholine.

Educational objective:
Chromaffin cells are modified neuroendocrine cells derived from the neural crest. Chromaffin cells in the adrenal

https://t.me/USMLEWorldStep1

2. The zona fasciculata is the middle zone and contains foamy-appearing cells in columns (*fascis* is Latin for bundle or stack) that secrete glucocorticoid hormones (primarily cortisol).
3. The zona reticularis is the inner zone of the cortex and contains cells in anastomosing cords (*rete* is Latin for net) that secrete androgens.
4. The **adrenal medulla** is sharply demarcated from the cortex and is composed of chromaffin cells with a deeply basophilic cytoplasm.

Chromaffin cells are modified neuroendocrine cells derived from the neural crest. They are **stimulated by acetylcholine** released by sympathetic preganglionic neurons and **secrete catecholamines** (80% epinephrine, 20% norepinephrine) directly into the bloodstream to amplify sympathetic nervous system activity.

(Choice B) ACTH stimulates secretion of glucocorticoid hormones from the zona fasciculata. Cortisol produced in response to ACTH increases activity of the adrenal medullary enzyme phenylethanolamine N-methyltransferase, which catalyzes the conversion of norepinephrine to epinephrine. ACTH therefore indirectly upregulates medullary epinephrine production, but does not directly control it.

(Choice C) Aldosterone secretion from the zona glomerulosa is primarily regulated by angiotensin II and extracellular potassium levels.

(Choice D) Epinephrine released by the adrenal medulla acts on adrenergic receptors in the heart, lungs, liver, and skeletal muscle to increase sympathetic tone and mediate the acute stress response.

(Choice E) Most sympathetic *postganglionic* neurons release norepinephrine to activate adrenergic receptors on the target tissues. However, the *preganglionic* fibers innervating the adrenal medulla (and postganglionic sympathetic neurons innervating eccrine sweat glands) release acetylcholine.

Educational objective:
Chromaffin cells are modified neuroendocrine cells derived from the neural crest. Chromaffin cells in the adrenal medulla are stimulated by acetylcholine released by sympathetic preganglionic neurons and secrete catecholamines directly into the bloodstream to amplify sympathetic nervous system activity.

Histology Endocrine, Diabetes & Metabolism Pheochromocytoma

https://t.me/USMLEWorldStep1

A 54-year-old woman comes to the office for evaluation of elevated blood glucose. The patient was recently seen at an urgent care center, where she was found to have a nonfasting blood glucose level of 190 mg/dL. Medical history is insignificant, although she has not seen a physician for several years. She does not use tobacco or alcohol. BMI is 31.5 kg/m^2. Physical examination shows no abnormalities. Hemoglobin A1c is 8.5% and fasting plasma glucose level is 146 mg/dL. Recommendations for dietary modification and exercise are provided, and pharmacotherapy with metformin is planned. Which of the following laboratory tests should be obtained prior to starting this medication?

- A. Blood cell counts and mean corpuscular volume
- B. Oral glucose tolerance test
- C. Plasma lactate level
- D. Serum creatinine level
- E. Serum potassium level
- F. Serum TSH level

Submit

https://t.me/USMLEWorldStep1

A 54-year-old woman comes to the office for evaluation of elevated blood glucose. The patient was recently seen at an urgent care center, where she was found to have a nonfasting blood glucose level of 190 mg/dL. Medical history is insignificant, although she has not seen a physician for several years. She does not use tobacco or alcohol. BMI is 31.5 kg/m^2. Physical examination shows no abnormalities. Hemoglobin A1c is 8.5% and fasting plasma glucose level is 146 mg/dL. Recommendations for dietary modification and exercise are provided, and pharmacotherapy with metformin is planned. Which of the following laboratory tests should be obtained prior to starting this medication?

- A. Blood cell counts and mean corpuscular volume (3%)
- ✗ B. Oral glucose tolerance test (2%)
- C. Plasma lactate level (31%)
- ✓ D. Serum creatinine level (55%)
- E. Serum potassium level (3%)
- F. Serum TSH level (2%)

Incorrect
Correct answer
D

55%
Answered correctly

04 secs
Time Spent

2023
Version

Explanation

Metformin	
Mechanism of action	• Inhibits mitochondrial glycerophosphate dehydrogenase • Upregulates AMP-activated protein kinase
	• ↓ Hepatic glucose production • ↓ Intestinal glucose absorption

https://t.me/USMLEWorldStep1

Explanation

Metformin	
Mechanism of action	• Inhibits mitochondrial glycerophosphate dehydrogenase • Upregulates AMP-activated protein kinase
Metabolic effects	• ↓ Hepatic glucose production • ↓ Intestinal glucose absorption • ↑ Peripheral glucose uptake/utilization • ↓ Lipogenesis
Pharmacokinetics	• Renal clearance • No significant metabolites
Adverse effects	• Diarrhea • Lactic acidosis • Vitamin B_{12} deficiency
Precautions/ contraindications	• Renal insufficiency (check serum creatinine) • Hepatic insufficiency • Decompensated heart failure

Metformin lowers blood glucose by decreasing hepatic gluconeogenesis and increasing insulin-dependent peripheral glucose uptake. It functions by inhibiting mitochondrial glycerol-3-phosphate dehydrogenase, which **reduces** availability of **gluconeogenesis substrates** (eg, glycerol, lactate). Metformin also upregulates AMP-activated protein kinase, which inhibits lipogenesis and subsequently lowers circulating lipid levels.

Metformin is the preferred first-line medication for type 2 diabetes mellitus. It does not increase endogenous insulin secretion and therefore carries a **low risk of hypoglycemia**. In addition, it also leads to **modest weight loss** in most patients.

However, the inhibition of gluconeogenesis by metformin results in increased lactate production. Patients with

https://t.me/USMLEWorldStep1

Metformin lowers blood glucose by decreasing hepatic gluconeogenesis and increasing insulin-dependent peripheral glucose uptake. It functions by inhibiting mitochondrial glycerol-3-phosphate dehydrogenase, which **reduces** availability of **gluconeogenesis substrates** (eg, glycerol, lactate). Metformin also upregulates AMP-activated protein kinase, which inhibits lipogenesis and subsequently lowers circulating lipid levels.

Metformin is the preferred first-line medication for type 2 diabetes mellitus. It does not increase endogenous insulin secretion and therefore carries a **low risk of hypoglycemia**. In addition, it also leads to **modest weight loss** in most patients.

However, the inhibition of gluconeogenesis by metformin results in increased lactate production. Patients with significant renal dysfunction or other disorders that reduce lactate clearance (eg, hepatic impairment) are at risk for metformin-induced **lactic acidosis**. For this reason, the glomerular filtration rate should be estimated using **serum creatinine measurement** prior to the initiation of metformin.

(Choice A) Metformin can cause vitamin B_{12} deficiency (leading to macrocytic anemia), likely due to decreased intestinal absorption. However, this is a chronic effect seen after long-term use, and pretreatment testing is not needed.

(Choice B) The oral glucose tolerance test is used for the initial diagnosis of diabetes mellitus, primarily gestational diabetes. This patient's diagnosis has been confirmed with elevated fasting glucose and hemoglobin A1c; additional diagnostic testing is not necessary.

(Choice C) Plasma lactate levels are used to confirm acute lactic acidosis; measurement of a baseline level is not useful.

(Choice E) Monitoring serum potassium is not necessary with metformin use. Serum potassium is routinely monitored with diuretics (especially loop diuretics), spironolactone, ACE inhibitors, and angiotensin II receptor blockers.

(Choice F) Thyroid function tests routinely performed in patients taking lithium and amiodarone but are not required for antidiabetic medications, including metformin.

Educational objective:
Metformin lowers blood glucose by reducing hepatic gluconeogenesis and increasing insulin-dependent peripheral

https://t.me/USMLEWorldStep1

activated protein kinase, which inhibits lipogenesis and subsequently lowers circulating lipid levels.

Metformin is the preferred first-line medication for type 2 diabetes mellitus. It does not increase endogenous insulin secretion and therefore carries a **low risk of hypoglycemia**. In addition, it also leads to **modest weight loss** in most patients.

However, the inhibition of gluconeogenesis by metformin results in increased lactate production. Patients with significant renal dysfunction or other disorders that reduce lactate clearance (eg, hepatic impairment) are at risk for metformin-induced **lactic acidosis**. For this reason, the glomerular filtration rate should be estimated using **serum creatinine measurement** prior to the initiation of metformin.

(Choice A) Metformin can cause vitamin B_{12} deficiency (leading to macrocytic anemia), likely due to decreased intestinal absorption. However, this is a chronic effect seen after long-term use, and pretreatment testing is not needed.

(Choice B) The oral glucose tolerance test is used for the initial diagnosis of diabetes mellitus, primarily gestational diabetes. This patient's diagnosis has been confirmed with elevated fasting glucose and hemoglobin A1c; additional diagnostic testing is not necessary.

(Choice C) Plasma lactate levels are used to confirm acute lactic acidosis; measurement of a baseline level is not useful.

(Choice E) Monitoring serum potassium is not necessary with metformin use. Serum potassium is routinely monitored with diuretics (especially loop diuretics), spironolactone, ACE inhibitors, and angiotensin II receptor blockers.

(Choice F) Thyroid function tests routinely performed in patients taking lithium and amiodarone but are not required for antidiabetic medications, including metformin.

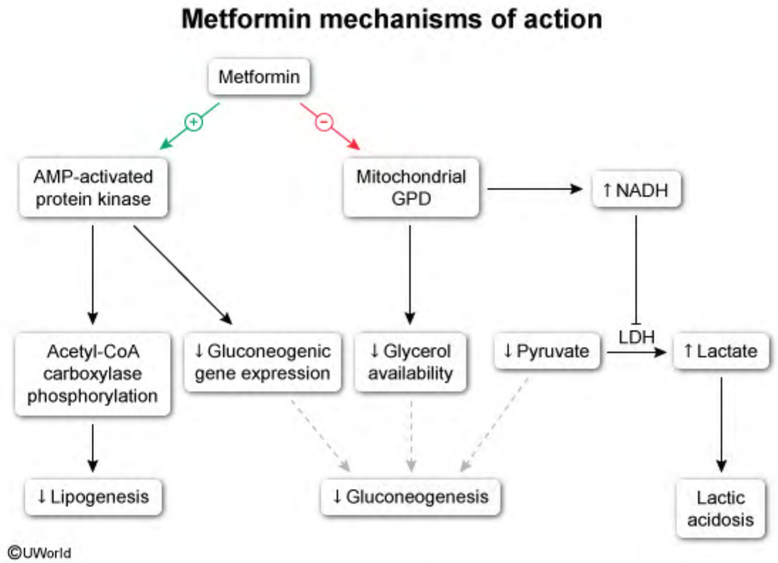
Educational objective:
Metformin lowers blood glucose by reducing hepatic gluconeogenesis and increasing insulin-dependent peripheral glucose uptake. Lactic acidosis is a rare complication of metformin therapy; the risk is increased in patients with underlying renal insufficiency.

References

https://t.me/USMLEWorldStep1

- Diarrhea

Exhibit Display



Zoom In Zoom Out Reset New | Existing My Notebook

Metfo
periph
reduc
activat

Metfor
insulin
loss ir

Howev
signifi
metfor
creati

(Choi
intesti
neede

(Choi
gestat
A1c; a

(Choi
useful.

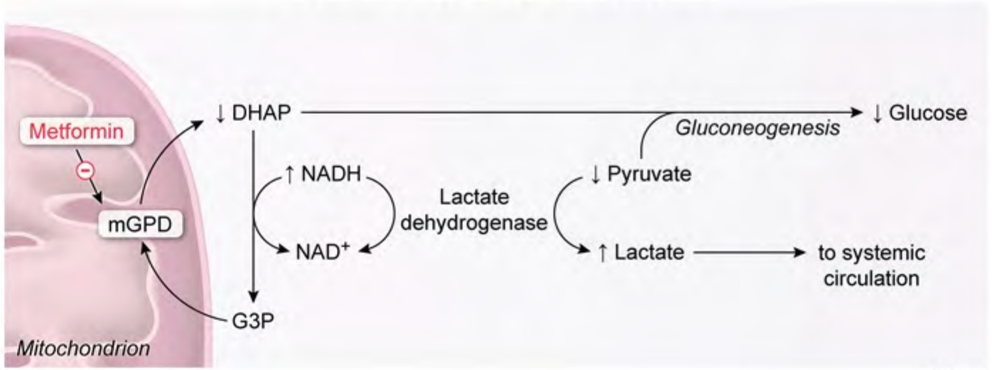
(Choice E) Monitoring serum potassium is not necessary with metformin use. Serum potassium is routinely

https://t.me/USMLEWorldStep1

- Diarrhea

Exhibit Display

Mechanism of action of metformin



©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Metfo
periph
reduc
activat

Metfor
insulin
loss ir

Howev
signifi
metfor
creati

(Choi
intesti
neede

(Choi
gestat
A1c; a

(Choi
useful.

(Choice E) Monitoring serum potassium is not necessary with metformin use. Serum potassium is routinely

https://t.me/USMLEWorldStep1

A 7-year-old boy is brought to the clinic for a well-child visit. Over the past year, the patient has become fidgety, impulsive, inattentive, and restless, leading to a progressive decline in his grades. Height and weight are at the 50th and 5th percentiles for his age, respectively. The patient takes no medications or supplements. The thyroid gland is diffusely enlarged to palpation without tenderness or bruit. Neurologic examination reveals no focal findings. Results of thyroid function tests are as follows:

TSH	7 mU/L
Thyroxine, total	16 µg/dL
Triiodothyronine	210 ng/dL (normal: 80-195)

Which of the following is the most likely etiology of this patient's thyroid function test abnormalities?

- A. Chronic autoimmune thyroiditis
- B. Elevated thyroxine-binding globulin
- C. Graves disease
- D. Organification defect in thyroid hormone synthesis
- E. Resistance to thyroid hormone

Submit

https://t.me/USMLEWorldStep1

A 7-year-old boy is brought to the clinic for a well-child visit. Over the past year, the patient has become fidgety, impulsive, inattentive, and restless, leading to a progressive decline in his grades. Height and weight are at the 50th and 5th percentiles for his age, respectively. The patient takes no medications or supplements. The thyroid gland is diffusely enlarged to palpation without tenderness or bruit. Neurologic examination reveals no focal findings. Results of thyroid function tests are as follows:

TSH	7 mU/L
Thyroxine, total	16 µg/dL
Triiodothyronine	210 ng/dL (normal: 80-195)

Which of the following is the most likely etiology of this patient's thyroid function test abnormalities?

- A. Chronic autoimmune thyroiditis (11%)
- ✗ B. Elevated thyroxine-binding globulin (15%)
- C. Graves disease (22%)
- D. Organification defect in thyroid hormone synthesis (7%)
- ✓ E. Resistance to thyroid hormone (43%)

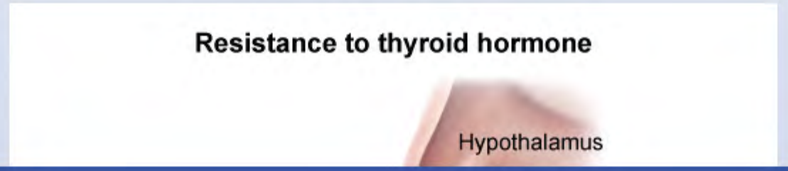
Incorrect
Correct answer
E

43%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation



https://t.me/USMLEWorldStep1

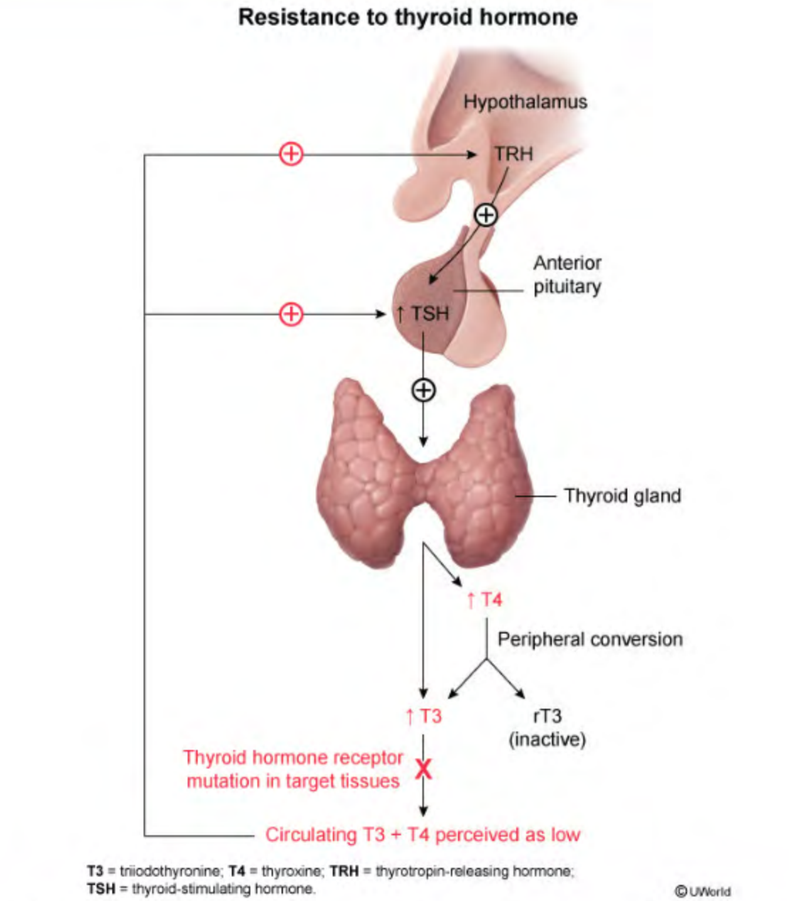
A 7-year-old boy is brought to the clinic for a well-child visit. Over the past year, the patient has become fidgety, impuls
50th a
gland
finding

Which

Inco
Corre
E

Expl

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Hypothalamus

https://t.me/USMLEWorldStep1

This patient's **increased** levels of **thyroxine (T4)**, **triiodothyronine (T3)**, and **TSH** are concerning for **thyroid hormone resistance**. Most cases are due to an inherited mutation affecting **thyroid hormone receptor beta**, which results in **decreased thyroid hormone sensitivity** in the hypothalamic-pituitary-thyroid axis and peripheral tissues. Increased levels of T3 and T4 normally provide negative feedback to the pituitary to decrease TSH production. However, because pituitary cells are also resistant to thyroid hormone in this condition, TSH rises, driving further production of T3 and T4.

The presentation of thyroid hormone resistance varies greatly due to fluctuating thyroid hormone sensitivity in different target tissues; patients may be asymptomatic (ie, euthyroid) or develop hypothyroid or hyperthyroid symptoms (eg, low weight, as in this patient). The most common finding is **goiter** due to overstimulation of the thyroid gland by TSH. **Attention deficit hyperactivity disorder** (ADHD) and **tachycardia** are also common due to the preponderance of alpha thyroid hormone receptors (with normal sensitivity) in the CNS and heart.

(Choice A) Chronic autoimmune (Hashimoto) thyroiditis leads to autoantibody-mediated thyroid gland destruction characterized by goiter and symptoms of hypothyroidism (eg, fatigue, constipation, dry skin). Low T3 and T4 production results in increased TSH.

(Choice B) Thyroxine-binding globulin (TBG) binds thyroid hormones and maintains a constant pool of free T3 and T4. Increases in TBG (eg, pregnancy) result in a clinically euthyroid, asymptomatic state characterized by an increased total T3 and T4 but normal levels of free hormones and TSH.

(Choice C) TSH receptor–stimulating antibodies in Graves disease cause increased T3 and T4 production with signs of hyperthyroidism, including goiter. In contrast to this patient, those with this condition have appropriate negative feedback to the pituitary, leading to low TSH levels.

(Choice D) Defective thyroid hormone synthesis leads to overt hypothyroidism starting in infancy; symptoms include lethargy, hypotonia, and constipation. Laboratory evaluation shows low T3 and T4 and elevated TSH.

Educational objective:
Thyroid hormone resistance is characterized by decreased sensitivity of peripheral tissues to thyroid hormones due to a defect in the thyroid hormone receptor. Levels of thyroxine, triiodothyronine, and TSH are increased. Patients classically have goiter and frequently develop attention deficit hyperactivity disorder.

https://t.me/USMLEWorldStep1

This patient's **increased** levels of **thyroxine (T4)**, **triiodothyronine (T3)**, and **TSH** are concerning for **thyroid**

hormo

which

tissues

produc

drivin

The pr

differe

sympt

thyroic

to the

(Choi

charac

produc

(Choi

and T4

increa

(Choi

signs

negati

(Choi

include

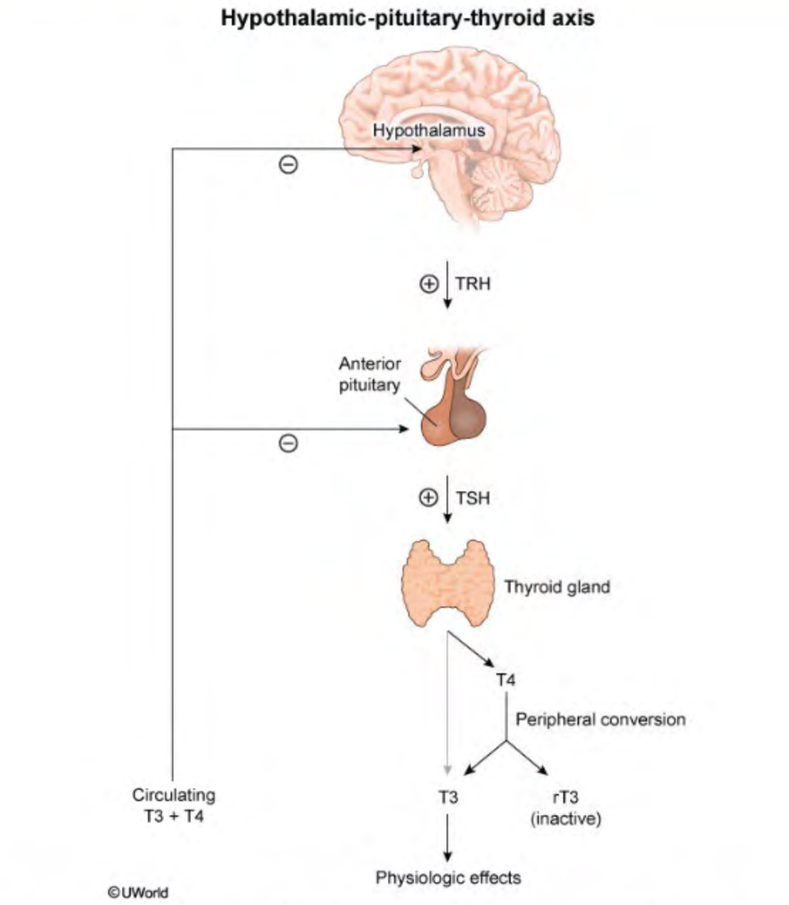
Educa

Thyroi

to a de

classically have goiter and frequently develop attention deficit hyperactivity disorder.

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

This patient's **increased** levels of **thyroxine (T4)**, **triiodothyronine (T3)**, and **TSH** are concerning for **thyroid**

hormo

which

tissues

produc

driving

The pr

differe

sympt

thyroic

to the

(Choi

charac

produc

(Choi

and T4

increa

(Choi

signs

negati

(Choi

include

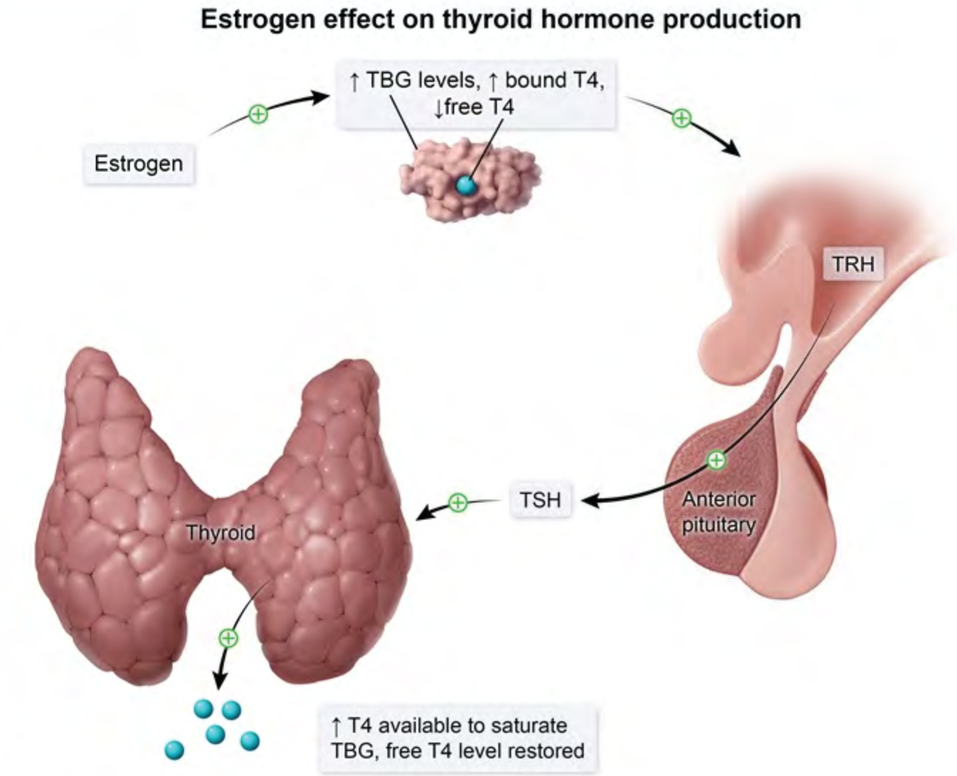
Educa

Thyroi

to a de

classically have goiter and frequently develop attention deficit hyperactivity disorder.

Exhibit Display



Zoom In Zoom Out Reset New | Existing My Notebook

https://t.me/USMLEWorldStep1

A 64-year-old man comes to the office due to a 6-month history of difficulty urinating, with frequent straining and dribbling. His symptoms have increased over time and affect his quality of life significantly. The physician prescribes a drug that gives the patient moderate symptomatic relief. However, he also experiences a decrease in libido and impaired erectile function. Which of the following is the most likely mechanism of action of this patient's medication?

- A. Decreased dihydrotestosterone synthesis
- B. Decreased Leydig cell androgen synthesis
- C. Decreased Leydig cell stimulation by LH
- D. Decreased peripheral androgen aromatization
- E. Impaired androgen-receptor interaction
- F. Impaired second messenger action

Submit

https://t.me/USMLEWorldStep1

A 64-year-old man comes to the office due to a 6-month history of difficulty urinating, with frequent straining and dribbling. His symptoms have increased over time and affect his quality of life significantly. The physician prescribes a drug that gives the patient moderate symptomatic relief. However, he also experiences a decrease in libido and impaired erectile function. Which of the following is the most likely mechanism of action of this patient's medication?

- ✓ A. Decreased dihydrotestosterone synthesis (57%)
- B. Decreased Leydig cell androgen synthesis (5%)
- ✗ C. Decreased Leydig cell stimulation by LH (6%)
- D. Decreased peripheral androgen aromatization (8%)
- E. Impaired androgen-receptor interaction (14%)
- F. Impaired second messenger action (8%)

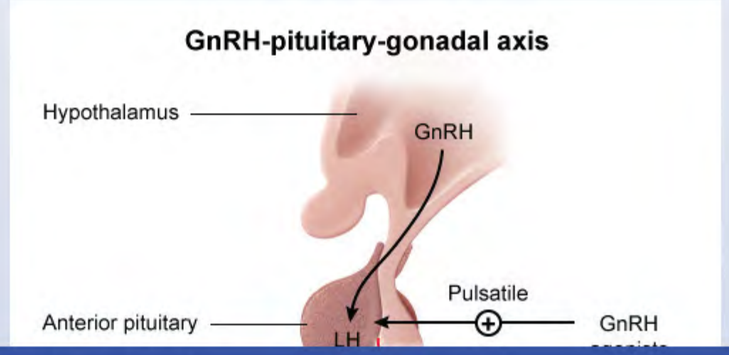
Incorrect
Correct answer
A

57%
Answered correctly

03 secs
Time Spent

2023
Version

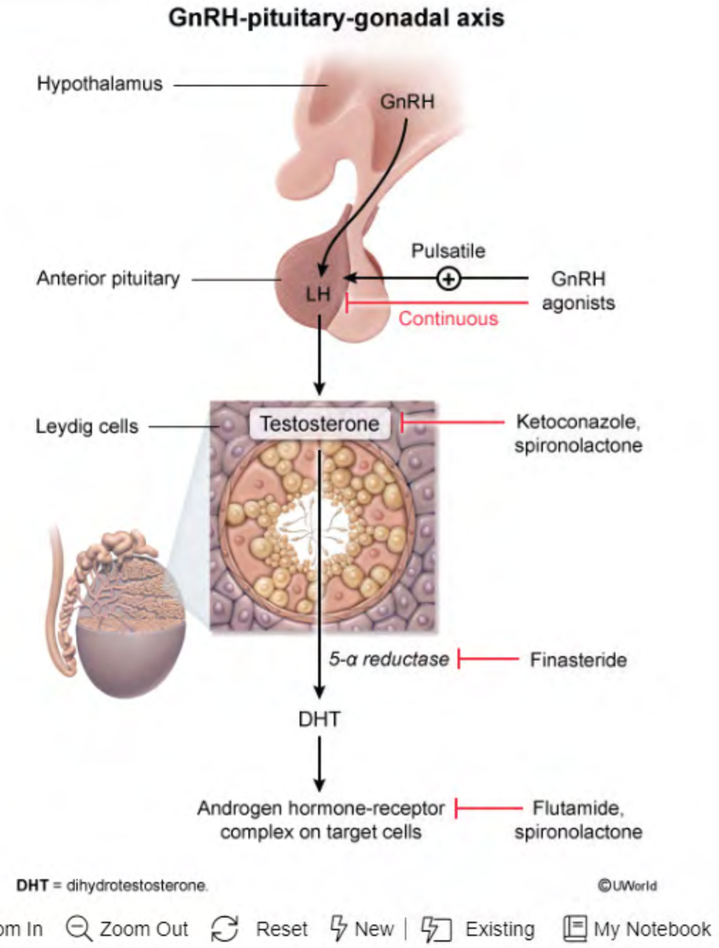
Explanation



https://t.me/USMLEWorldStep1

A 64-year-old man comes to the office due to a 6-month history of difficulty urinating, with frequent straining and dribbli
prescr
libido
medic

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Anterior pituitary
LH
Pulsatile
GnRH

https://t.me/USMLEWorldStep1

DHT = dihydrotestosterone.

©UWorld

This patient has **benign prostatic hyperplasia** (BPH) with lower urinary tract symptoms (eg, hesitancy, dribbling). BPH is characterized by an increase in glandular volume, which obstructs urine flow in the prostatic urethra. Prostate enlargement in BPH is driven primarily by **dihydrotestosterone** (DHT), which is derived from testosterone by **5-alpha-reductase** (5AR) in peripheral tissues. DHT has a much higher affinity than testosterone for the androgen receptor and mediates the majority of testosterone effects.

5AR inhibitors (eg, finasteride) are antiandrogen agents that reduce conversion of testosterone to DHT. In men with BPH, 5AR inhibitors induce a gradual **reduction in prostate volume**, improving urinary flow. However, they are associated with significant **androgen-deficiency effects**, including decreased libido, erectile dysfunction, and decreased ejaculate volume. In addition, the residual testosterone is available for conversion by aromatase to estradiol, leading to gynecomastia.

(Choices B and C) Long-acting gonadotropin-releasing hormone (GnRH) analogues (eg, leuprolide) suppress pituitary LH secretion, leading to decreased testosterone production in Leydig cells. Steroid synthesis inhibitors (eg, ketoconazole) directly reduce testosterone production in the testes. However, 5AR inhibitors affect peripheral testosterone metabolism, not testosterone production.

(Choice D) Aromatase inhibitors (eg, anastrozole) decrease conversion of androgens to the corresponding estrogens and are primarily used in treatment of hormone receptor–positive breast cancer in women. These agents are not used for BPH.

(Choice E) The interaction of testosterone and DHT with the androgen receptor is inhibited by flutamide and spironolactone. These agents have significant feminizing effects (eg, gynecomastia) and are not used in BPH.

(Choice F) The androgen receptor primarily acts as a DNA-binding transcription factor and does not require second messenger action. 5AR inhibitors do not have a significant effect on second messenger systems.

Educational objective:
5-alpha-reductase inhibitors (eg, finasteride) reduce conversion of testosterone to dihydrotestosterone. In men with benign prostatic hyperplasia, these agents reduce prostate volume and alleviate obstruction of urinary flow. However, they are associated with androgen-deficiency effects, including decreased libido, erectile dysfunction, and decreased ejaculate volume.

https://t.me/USMLEWorldStep1

DHT = dihydrotestosterone.

©UWorld

This patient has **benign prostatic hyperplasia** (BPH) with lower urinary tract symptoms (eg, hesitancy, dribbling).

BPH is

Prosta

testost

for the

5AR i

with B

are as

decrea

estrad

(Choi

pituita

(eg, ke

testost

(Choi

estrog

agents

(Choi

spiron

(Choi

secon

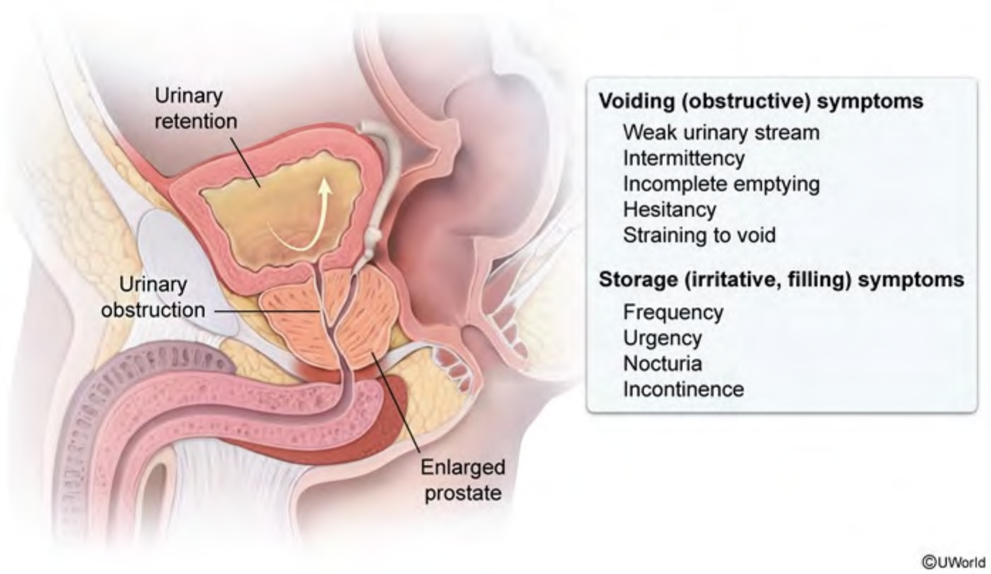
Educa

5-alph

with be

However, they are associated with androgen-deficiency effects, including decreased libido, erectile dysfunction, and decreased ejaculate volume.

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

An 18-month-old boy is brought to clinic due to difficulty walking. The patient began walking around age 12 months but his mother recently noticed he has difficulty maintaining his balance and often falls after a few steps. Weight is at the 15th percentile and height is at the 5th percentile. Examination shows increased tone with occasional muscle spasms in the lower extremities. Abdominal examination shows hepatosplenomegaly. Laboratory results reveal decreased glucocerebrosidase activity. This patient's enzyme deficiency is most likely impairing the function of which of the following organelles?

- A. Golgi apparatus
- B. Lysosomes
- C. Mitochondria
- D. Peroxisomes
- E. Proteasomes
- F. Ribosomes

Submit

https://t.me/USMLEWorldStep1

An 18-month-old boy is brought to clinic due to difficulty walking. The patient began walking around age 12 months but his mother recently noticed he has difficulty maintaining his balance and often falls after a few steps. Weight is at the 15th percentile and height is at the 5th percentile. Examination shows increased tone with occasional muscle spasms in the lower extremities. Abdominal examination shows hepatosplenomegaly. Laboratory results reveal decreased glucocerebrosidase activity. This patient's enzyme deficiency is most likely impairing the function of which of the following organelles?

- A. Golgi apparatus (3%)
- ✓ B. Lysosomes (81%)
- ✗ C. Mitochondria (6%)
- D. Peroxisomes (5%)
- E. Proteasomes (1%)
- F. Ribosomes (1%)

Incorrect
Correct answer
B

81%
Answered correctly

04 secs
Time Spent

2023
Version

Explanation

Sphingolipidoses*

Diagnosis	Inheritance	Deficiency	Accumulated substrate	Key features
Fabry disease	XLR	α-Galactosidase A	Globotriaosylceramide	• Angiokeratomas • Peripheral neuropathy • Glomerulopathy

https://t.me/USMLEWorldStep1

Sphingolipidoses*				
Diagnosis	**Inheritance**	**Deficiency**	**Accumulated substrate**	**Key features**
Fabry disease	XLR	α-Galactosidase A	Globotriaosylceramide	• Angiokeratomas • Peripheral neuropathy • Glomerulopathy
Tay-Sachs disease	AR	β-Hexosaminidase A	G_{M2} (ganglioside)	• Macular cherry-red spot • Progressive neurodegeneration
Gaucher disease		β-Glucocerebrosidase	Glucocerebroside	• Hepatosplenomegaly • Pancytopenia • Bone pain/osteopenia
Niemann-Pick disease		Sphingomyelinase	Sphingomyelin	• Macular cherry-red spot • Progressive neurodegeneration • Hepatosplenomegaly
Krabbe disease		Galactocerebrosidase	Galactocerebroside & psychosine	• Progressive neurodegeneration • Peripheral neuropathy • Optic atrophy
Metachromatic leukodystrophy		Arylsulfatase A	Cerebroside sulfate	• Progressive neurodegeneration

https://t.me/USMLEWorldStep1

Diagnosis	Inheritance	Deficiency	Accumulated substrate	Key features
Fabry disease	XLR	α-Galactosidase A	Globotriaosylceramide	• Angiokeratomas • Peripheral neuropathy • Glomerulopathy
Tay-Sachs disease	AR	β-Hexosaminidase A	G_{M2} (ganglioside)	• Macular cherry-red spot • Progressive neurodegeneration
Gaucher disease		β-Glucocerebrosidase	Glucocerebroside	• Hepatosplenomegaly • Pancytopenia • Bone pain/osteopenia
Niemann-Pick disease		Sphingomyelinase	Sphingomyelin	• Macular cherry-red spot • Progressive neurodegeneration • Hepatosplenomegaly
Krabbe disease		Galactocerebrosidase	Galactocerebroside & psychosine	• Progressive neurodegeneration • Peripheral neuropathy • Optic atrophy
Metachromatic leukodystrophy		Arylsulfatase A	Cerebroside sulfate	• Progressive neurodegeneration • Peripheral neuropathy

* Subtype of lysosomal storage disorder.

AR = autosomal recessive; **XLR** = X-linked recessive.

https://t.me/USMLEWorldStep1

* Subtype of lysosomal storage disorder.

AR = autosomal recessive; **XLR** = X-linked recessive.

Glucocerebrosidase is an acid hydrolase (enzyme active at a low pH) that is found within **lysosomes**; it is responsible for the breakdown of glucocerebroside, a component of cell membranes. Decreased activity of this enzyme occurs in **Gaucher disease** and results in the accumulation of glucocerebroside in lysosomes, which disrupts cellular function. Because **mononuclear phagocytes** (eg, macrophages) engulf cellular debris and extracellular matrix components, they are affected in most lysosomal storage diseases (eg, sphingolipidoses, mucopolysaccharidoses), including Gaucher disease.

In Gaucher disease, macrophages in the liver, spleen, and bone are predominantly affected, resulting in marked **hepatosplenomegaly** (as seen here), bone marrow replacement (eg, anemia, thrombocytopenia), **bone pain**, and **poor growth** (eg, height ≤5th percentile). The CNS is also susceptible to glucocerebroside accumulation, and some patients may have **neurologic** manifestations such as this child's spasticity, muscle spasms, and loss of motor skills.

(Choices A and F) Golgi apparatus defects lead to improper sorting and post-translational glycosylation of cellular proteins, and ribosomal abnormalities would result in deficient protein production. Decreased glucocerebrosidase activity is not associated with such defects.

(Choice C) The mitochondria are responsible for ATP production, and diseases due to abnormal mitochondrial function most commonly lead to muscle weakness, hypotonia, and encephalopathy. Mitochondrial diseases are not associated with decreased glucocerebrosidase activity.

(Choice D) Enzymes within peroxisomes are critical in very long-chain fatty acid oxidation. Enzyme deficiencies, such as in X-linked adrenoleukodystrophy, can result in progressive neurodegeneration and adrenal insufficiency. Glucocerebrosidase is a lysosomal, not peroxisomal, enzyme.

(Choice E) Proteasomes degrade unwanted and misfolded proteins as well as foreign intracellular proteins for display on major histocompatibility complex (MHC) class I molecules. Proteosome dysfunction can lead to protein aggregation but is not associated with glucocerebrosidase deficiency.

Educational objective:

Gaucher disease is a lysosomal storage disease in which decreased activity of glucocerebrosidase leads to a

https://t.me/USMLEWorldStep1

extracellular matrix components, they are affected in most lysosomal storage diseases (eg, sphingolipidoses, mucopolysaccharidoses), including Gaucher disease.

In Gaucher disease, macrophages in the liver, spleen, and bone are predominantly affected, resulting in marked **hepatosplenomegaly** (as seen here), bone marrow replacement (eg, anemia, thrombocytopenia), **bone pain**, and **poor growth** (eg, height ≤5th percentile). The CNS is also susceptible to glucocerebroside accumulation, and some patients may have **neurologic** manifestations such as this child's spasticity, muscle spasms, and loss of motor skills.

(Choices A and F) Golgi apparatus defects lead to improper sorting and post-translational glycosylation of cellular proteins, and ribosomal abnormalities would result in deficient protein production. Decreased glucocerebrosidase activity is not associated with such defects.

(Choice C) The mitochondria are responsible for ATP production, and diseases due to abnormal mitochondrial function most commonly lead to muscle weakness, hypotonia, and encephalopathy. Mitochondrial diseases are not associated with decreased glucocerebrosidase activity.

(Choice D) Enzymes within peroxisomes are critical in very long-chain fatty acid oxidation. Enzyme deficiencies, such as in X-linked adrenoleukodystrophy, can result in progressive neurodegeneration and adrenal insufficiency. Glucocerebrosidase is a lysosomal, not peroxisomal, enzyme.

(Choice E) Proteasomes degrade unwanted and misfolded proteins as well as foreign intracellular proteins for display on major histocompatibility complex (MHC) class I molecules. Proteosome dysfunction can lead to protein aggregation but is not associated with glucocerebrosidase deficiency.

Educational objective:
Gaucher disease is a lysosomal storage disease in which decreased activity of glucocerebrosidase leads to a buildup of glucocerebroside. Accumulation of this substrate within lysosomes in the mononuclear phagocyte system classically results in hepatosplenomegaly, cytopenia, and bone pain; CNS involvement can also lead to neurologic manifestations (eg, spasticity).

Biochemistry	Endocrine, Diabetes & Metabolism	Gauchers Disease
Subject	System	Topic

https://t.me/USMLEWorldStep1

Metachromatic le		Arylsulfatase A	Cerebroside sulfate	• Progressive neurodegeneration

* S
AR

Gluco
respor
enzym
disrup
extrac
mucop

In Gau
hepat
poor g
some
motor

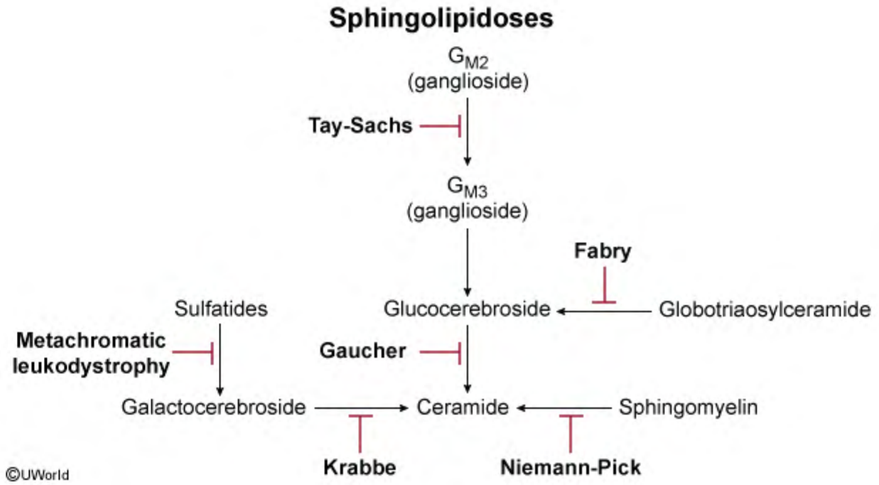
(Choi
protei
activity

(Choi
functio
not as

(Choi
such a
Glucoc

(Choice E) Proteasomes degrade unwanted and misfolded proteins as well as foreign intracellular proteins for

Exhibit Display

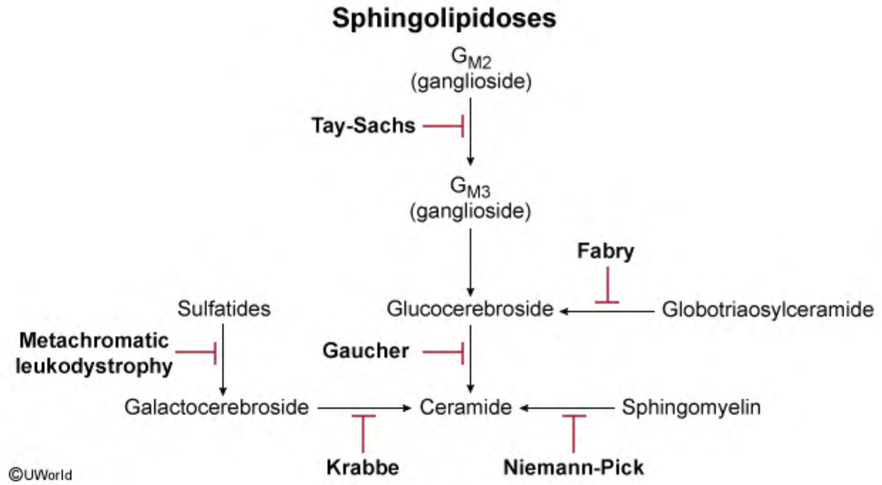


Zoom In Zoom Out Reset New | Existing My Notebook

https://t.me/USMLEWorldStep1

Metachromatic le		Arylsulfatase A	Cerebroside sulfate	• Progressive neurodegeneration

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Gluco
respor
enzym
disrup
extrac
mucop

In Gau
hepat
poor g
some
motor

(Choi
protein
activity

(Choi
functio
not as

(Choi
such a
Glucoc

(Choice E) Proteasomes degrade unwanted and misfolded proteins as well as foreign intracellular proteins for

https://t.me/USMLEWorldStep1

A 25-year-old woman is brought to the emergency department due to progressive lethargy. For the last 3 weeks, she has also had loss of appetite, constipation, muscle weakness, and increased thirst and urination. The patient's medical history is unremarkable. She takes no prescription medications but has been taking large doses of vitamin D supplements in the belief that they are beneficial for her health. The patient does not use tobacco, alcohol, or illicit drugs. On physical examination, she is stuporous and has dry mucous membranes. The metabolic abnormality most likely responsible for this patient's clinical findings can also occur in which of the following conditions?

- A. Biliary obstruction
- B. Carcinoid syndrome
- C. Hemochromatosis
- D. Pheochromocytoma
- E. Sarcoidosis
- F. Wilson disease

Submit

https://t.me/USMLEWorldStep1

A 25-year-old woman is brought to the emergency department due to progressive lethargy. For the last 3 weeks, she has also had loss of appetite, constipation, muscle weakness, and increased thirst and urination. The patient's medical history is unremarkable. She takes no prescription medications but has been taking large doses of vitamin D supplements in the belief that they are beneficial for her health. The patient does not use tobacco, alcohol, or illicit drugs. On physical examination, she is stuporous and has dry mucous membranes. The metabolic abnormality most likely responsible for this patient's clinical findings can also occur in which of the following conditions?

- ✗ A. Biliary obstruction (5%)
- B. Carcinoid syndrome (12%)
- C. Hemochromatosis (9%)
- D. Pheochromocytoma (6%)
- ✓ E. Sarcoidosis (60%)
- F. Wilson disease (4%)

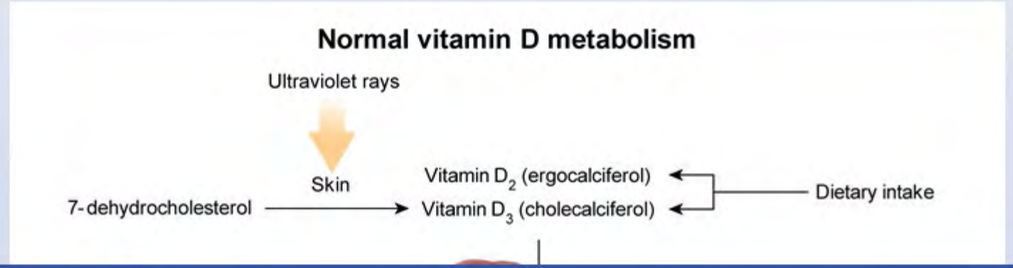
Incorrect
Correct answer
E

60%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

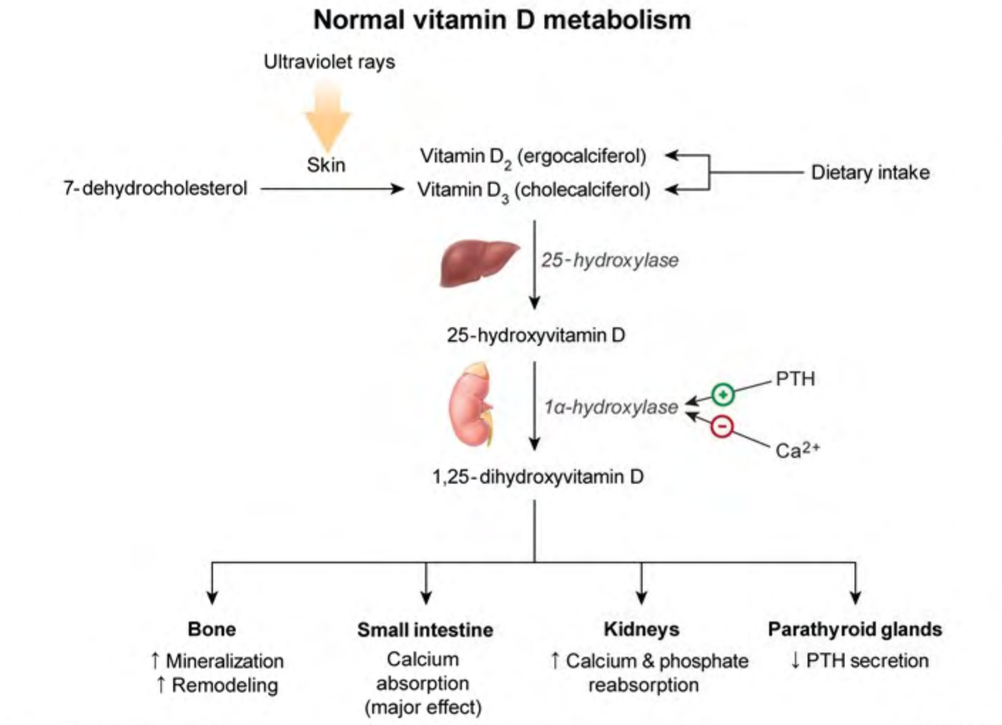


https://t.me/USMLEWorldStep1

Incorrect
Correct answer
E

60%
03 secs
2023

Exhibit Display



Zoom In Zoom Out Reset New | Existing My Notebook

Expl

Moder
minera
depola
concentration of urine in the distal tubule (**polyuria/polydipsia**). Chronic vitamin D intoxication can also lead to

https://t.me/USMLEWorldStep1

PTH = parathyroid hormone.

©UWorld

Moderate doses of vitamin D are often recommended for patients with inadequate dietary intake to improve bone mineralization. However, excessive vitamin D can cause symptomatic **hypercalcemia**, with impaired depolarization of neuromuscular membranes (eg, muscle **weakness**, **constipation**, **confusion**) and impaired concentration of urine in the distal tubule (**polyuria/polydipsia**). Chronic vitamin D intoxication can also lead to **renal stone formation** and bone demineralization with associated **bone pain** (although normal vitamin D levels facilitate bone mineralization, toxicity increases osteoclast activity and bone turnover).

Normally, 25-hydroxyvitamin D is converted to 1,25-dihydroxyvitamin D (the active form) by **1-α-hydroxylase** in the kidneys, a process regulated by parathyroid hormone (PTH). However, patients with **granulomatous diseases** (eg, sarcoidosis, tuberculosis) can have **PTH-independent conversion** due to expression of 1-α-hydroxylase in **activated macrophages**. A similar process can occur in Hodgkin disease and some non-Hodgkin lymphomas.

(Choice A) Biliary obstruction is associated with altered lipid absorption and deficiencies of fat-soluble vitamins (eg, A, D, E, and K).

(Choice B) Carcinoid tumor cells synthesize excessive amounts of serotonin. When these cells metastasize to the liver, the release of serotonin into the systemic circulation results in carcinoid syndrome (eg, episodic cutaneous flushing, bronchospasm/wheezing, diarrhea).

(Choice C) Hemochromatosis is associated with excessive intestinal absorption of iron and accumulation in parenchymal organs. Patients classically develop liver cirrhosis, heart failure, skin hyperpigmentation, and diabetes mellitus ("bronze diabetes").

(Choice D) Pheochromocytoma is associated with elevated levels of metanephrines and catecholamines. Patients typically have paroxysmal headache, diaphoresis, tachycardia, and hypertension.

(Choice F) Wilson disease (hepatolenticular degeneration) is characterized by impaired incorporation of copper into ceruloplasmin and defective excretion of excess copper into bile. This leads to elevated blood free copper levels and deposition in the liver (cirrhosis) and brain (motor abnormalities, psychiatric symptoms).

Educational objective:
Excessive vitamin D intake can lead to hypercalcemia and cause mental status changes, muscle weakness, constipation, and polyuria/polydipsia. Activated macrophages in sarcoidosis and other granulomatous diseases

https://t.me/USMLEWorldStep1

depolarization of neuromuscular membranes (eg, muscle **weakness**, **constipation**, **confusion**) and impaired concentration of urine in the distal tubule (**polyuria/polydipsia**). Chronic vitamin D intoxication can also lead to **renal stone formation** and bone demineralization with associated **bone pain** (although normal vitamin D levels facilitate bone mineralization, toxicity increases osteoclast activity and bone turnover).

Normally, 25-hydroxyvitamin D is converted to 1,25-dihydroxyvitamin D (the active form) by **1-α-hydroxylase** in the kidneys, a process regulated by parathyroid hormone (PTH). However, patients with **granulomatous diseases** (eg, sarcoidosis, tuberculosis) can have **PTH-independent conversion** due to expression of 1-α-hydroxylase in **activated macrophages**. A similar process can occur in Hodgkin disease and some non-Hodgkin lymphomas.

(Choice A) Biliary obstruction is associated with altered lipid absorption and deficiencies of fat-soluble vitamins (eg, A, D, E, and K).

(Choice B) Carcinoid tumor cells synthesize excessive amounts of serotonin. When these cells metastasize to the liver, the release of serotonin into the systemic circulation results in carcinoid syndrome (eg, episodic cutaneous flushing, bronchospasm/wheezing, diarrhea).

(Choice C) Hemochromatosis is associated with excessive intestinal absorption of iron and accumulation in parenchymal organs. Patients classically develop liver cirrhosis, heart failure, skin hyperpigmentation, and diabetes mellitus ("bronze diabetes").

(Choice D) Pheochromocytoma is associated with elevated levels of metanephrines and catecholamines. Patients typically have paroxysmal headache, diaphoresis, tachycardia, and hypertension.

(Choice F) Wilson disease (hepatolenticular degeneration) is characterized by impaired incorporation of copper into ceruloplasmin and defective excretion of excess copper into bile. This leads to elevated blood free copper levels and deposition in the liver (cirrhosis) and brain (motor abnormalities, psychiatric symptoms).

Educational objective:
Excessive vitamin D intake can lead to hypercalcemia and cause mental status changes, muscle weakness, constipation, and polyuria/polydipsia. Activated macrophages in sarcoidosis and other granulomatous diseases express 1-α-hydroxylase, leading to excess production of 1,25-dihydroxyvitamin D and hypercalcemia.

References

Vitamin D toxicity resulting from overzealous correction of vitamin D deficiency

https://t.me/USMLEWorldStep1

A 48-year-old woman comes to the office for follow-up of type 2 diabetes mellitus. She has had diabetes for 10 years with gradually worsening glycemic control despite taking multiple oral antidiabetic agents. Three months ago, the patient discontinued her oral medications (except for metformin) and started a daily injection of insulin glargine; she has had multiple visits with the diabetes educator since then to review injection technique and titrate up the dose. However, the patient reports a 4.5-kg (10-lb) weight gain since starting insulin. She says, "I feel like I need to eat more. If that's how insulin is going to be, then I don't want to continue it." Which of the following is the most appropriate response to this patient's statement?

- A. "Regular exercise can reduce insulin-induced weight gain. What are your current exercise habits?"
- B. "Some patients eat more after starting insulin because they fear their sugar may drop. Have you noticed that happening to you?"
- C. "Sometimes stress can increase your appetite. How are things in your life right now?"
- D. "Unfortunately, although insulin controls diabetes, it can cause weight gain. But the benefits outweigh the side effects."

Submit

https://t.me/USMLEWorldStep1

A 48-year-old woman comes to the office for follow-up of type 2 diabetes mellitus. She has had diabetes for 10 years with gradually worsening glycemic control despite taking multiple oral antidiabetic agents. Three months ago, the patient discontinued her oral medications (except for metformin) and started a daily injection of insulin glargine; she has had multiple visits with the diabetes educator since then to review injection technique and titrate up the dose. However, the patient reports a 4.5-kg (10-lb) weight gain since starting insulin. She says, "I feel like I need to eat more. If that's how insulin is going to be, then I don't want to continue it." Which of the following is the most appropriate response to this patient's statement?

✗ ◉ A. "Regular exercise can reduce insulin-induced weight gain. What are your current exercise habits?" (15%)

✓ ○ B. "Some patients eat more after starting insulin because they fear their sugar may drop. Have you noticed that happening to you?" (49%)

○ C. "Sometimes stress can increase your appetite. How are things in your life right now?" (18%)

○ D. "Unfortunately, although insulin controls diabetes, it can cause weight gain. But the benefits outweigh the side effects." (16%)

Incorrect
Correct answer
B

49%
Answered correctly

04 secs
Time Spent

2023
Version

Explanation

Insulin-induced weight gain	
Physiologic factors	• Increased peripheral glucose uptake • Increased adipose fatty acid uptake • Reduced renal glucose losses
	• Less rigorous dietary adherence

https://t.me/USMLEWorldStep1

Insulin-induced weight gain	
Physiologic factors	• Increased peripheral glucose uptake • Increased adipose fatty acid uptake • Reduced renal glucose losses
Behavioral factors	• Less rigorous dietary adherence • Eating/snacking in response to hypoglycemic symptoms
Patient counseling	• Review for changes in diet • Ask about hypoglycemic symptoms

Insulin therapy for diabetes mellitus commonly causes **weight gain** due to increased peripheral glucose uptake, increased adipose lipid deposition, and reduced renal glucose loss (due to normalization of blood glucose, which reduces the filtered glucose load). Behavioral factors, including snacking and less rigorous adherence to dietary recommendations, can also contribute. Weight gain is especially pronounced in patients with type 2 diabetes who typically have high circulating levels of insulin and preexisting obesity.

This patient has experienced weight gain after initiating a long-acting insulin analogue (ie, insulin glargine). Insulin normally suppresses appetite, but this patient reports **increased need to eat**, which suggests that the weight gain may not be simply due to the metabolic effects of insulin. Specifically, this patient may be eating more to suppress **feelings of hypoglycemia**.

To address this patient's insulin-induced weight gain, the clinician should obtain additional history to elicit the **patient's perspective** on appetite, recent changes in **dietary patterns**, and associated **hypoglycemic symptoms**. Once the causes are better understood, several strategies, including dietary modification and changes to the insulin regimen, can mitigate insulin-induced weight gain.

(Choice A) Periodic review of exercise habits is recommended for patients with diabetes. However, this patient has already stated that appetite is her primary concern, so this should be explored first.

(Choice C) Patients can gain weight due to a variety of factors. In addition to physiologic factors, stress often alters diet and exercise habits, leading to weight gain. However, this patient's weight gain is temporally associated with the initiation and titration of insulin, which makes insulin the most reasonable culprit. If the issue is not

https://t.me/USMLEWorldStep1

Patient counseling	• Review for changes in diet • Ask about hypoglycemic symptoms

Insulin therapy for diabetes mellitus commonly causes **weight gain** due to increased peripheral glucose uptake, increased adipose lipid deposition, and reduced renal glucose loss (due to normalization of blood glucose, which reduces the filtered glucose load). Behavioral factors, including snacking and less rigorous adherence to dietary recommendations, can also contribute. Weight gain is especially pronounced in patients with type 2 diabetes who typically have high circulating levels of insulin and preexisting obesity.

This patient has experienced weight gain after initiating a long-acting insulin analogue (ie, insulin glargine). Insulin normally suppresses appetite, but this patient reports **increased need to eat**, which suggests that the weight gain may not be simply due to the metabolic effects of insulin. Specifically, this patient may be eating more to suppress **feelings of hypoglycemia**.

To address this patient's insulin-induced weight gain, the clinician should obtain additional history to elicit the **patient's perspective** on appetite, recent changes in **dietary patterns**, and associated **hypoglycemic symptoms**. Once the causes are better understood, several strategies, including dietary modification and changes to the insulin regimen, can mitigate insulin-induced weight gain.

(Choice A) Periodic review of exercise habits is recommended for patients with diabetes. However, this patient has already stated that appetite is her primary concern, so this should be explored first.

(Choice C) Patients can gain weight due to a variety of factors. In addition to physiologic factors, stress often alters diet and exercise habits, leading to weight gain. However, this patient's weight gain is temporally associated with the initiation and titration of insulin, which makes insulin the most reasonable culprit. If the issue is not resolved after addressing the patient's insulin regimen, other factors can be explored.

(Choice D) Although the benefits of improved glycemic control with insulin generally outweigh the negative effects of weight gain, this statement does not address the patient's concerns and could miss an opportunity to improve the insulin program.

Educational objective:
Insulin can cause weight gain due to physiologic (eg, increased peripheral glucose uptake, reduced renal loss of

https://t.me/USMLEWorldStep1

Insulin therapy for diabetes mellitus commonly causes **weight gain** due to increased peripheral glucose uptake, increased adipose lipid deposition, and reduced renal glucose loss (due to normalization of blood glucose, which reduces the filtered glucose load). Behavioral factors, including snacking and less rigorous adherence to dietary recommendations, can also contribute. Weight gain is especially pronounced in patients with type 2 diabetes who typically have high circulating levels of insulin and preexisting obesity.

This patient has experienced weight gain after initiating a long-acting insulin analogue (ie, insulin glargine). Insulin normally suppresses appetite, but this patient reports **increased need to eat**, which suggests that the weight gain may not be simply due to the metabolic effects of insulin. Specifically, this patient may be eating more to suppress **feelings of hypoglycemia**.

To address this patient's insulin-induced weight gain, the clinician should obtain additional history to elicit the **patient's perspective** on appetite, recent changes in **dietary patterns**, and associated **hypoglycemic symptoms**. Once the causes are better understood, several strategies, including dietary modification and changes to the insulin regimen, can mitigate insulin-induced weight gain.

(Choice A) Periodic review of exercise habits is recommended for patients with diabetes. However, this patient has already stated that appetite is her primary concern, so this should be explored first.

(Choice C) Patients can gain weight due to a variety of factors. In addition to physiologic factors, stress often alters diet and exercise habits, leading to weight gain. However, this patient's weight gain is temporally associated with the initiation and titration of insulin, which makes insulin the most reasonable culprit. If the issue is not resolved after addressing the patient's insulin regimen, other factors can be explored.

(Choice D) Although the benefits of improved glycemic control with insulin generally outweigh the negative effects of weight gain, this statement does not address the patient's concerns and could miss an opportunity to improve the insulin program.

Educational objective:
Insulin can cause weight gain due to physiologic (eg, increased peripheral glucose uptake, reduced renal loss of glucose) and behavioral (eg, increased snacking in response to hypoglycemia, less rigorous attention to diet) factors. Counseling should elicit the patient's perspective on appetite, changes in dietary patterns, and hypoglycemic symptoms.

https://t.me/USMLEWorldStep1

A 1-week-old boy is brought to the emergency department due to recurrent vomiting and poor feeding. The infant was born at term via spontaneous vaginal delivery with no complications. Temperature is 36.7 C (98 F), blood pressure is 58/30 mm Hg, pulse is 180/min, and respirations are 40/min. On examination, the patient is tired appearing with a sunken anterior fontanelle and dry mucous membranes. The remainder of the examination is unremarkable. Laboratory results are as follows:

Serum chemistry

Sodium	122 mEq/L
Potassium	5.7 mEq/L
Blood urea nitrogen	25 mg/dL
Creatinine	0.6 mg/dL

Which of the following additional laboratory findings are most likely to be seen in this patient?

	Cortisol	Aldosterone	Serum ACTH	17-hydroxyprogesterone
○ A.	↓	↓	↑	↑
○ B.	↓	↑	↑	↓
○ C.	↓	↓	↑	↓
○ D.	↓	↓	↓	↑
○ E.	↑	↓	↑	↑

Submit

https://t.me/USMLEWorldStep1

A 1-week-old boy is brought to the emergency department due to recurrent vomiting and poor feeding. The infant was born at term via spontaneous vaginal delivery with no complications. Temperature is 36.7 C (98 F), blood pressure is 58/30 mm Hg, pulse is 180/min, and respirations are 40/min. On examination, the patient is tired appearing with a sunken anterior fontanelle and dry mucous membranes. The remainder of the examination is unremarkable. Laboratory results are as follows:

Serum chemistry

Sodium	122 mEq/L
Potassium	5.7 mEq/L
Blood urea nitrogen	25 mg/dL
Creatinine	0.6 mg/dL

Which of the following additional laboratory findings are most likely to be seen in this patient?

	Cortisol	Aldosterone	Serum ACTH	17-hydroxyprogesterone	
✓ A.	↓	↓	↑	↑	(64%)
B.	↓	↑	↑	↓	(7%)
C.	↓	↓	↑	↓	(16%)
D.	↓	↓	↓	↑	(5%)
E.	↑	↓	↑	↑	(6%)

Correct

64% Answered correctly

28 secs Time Spent

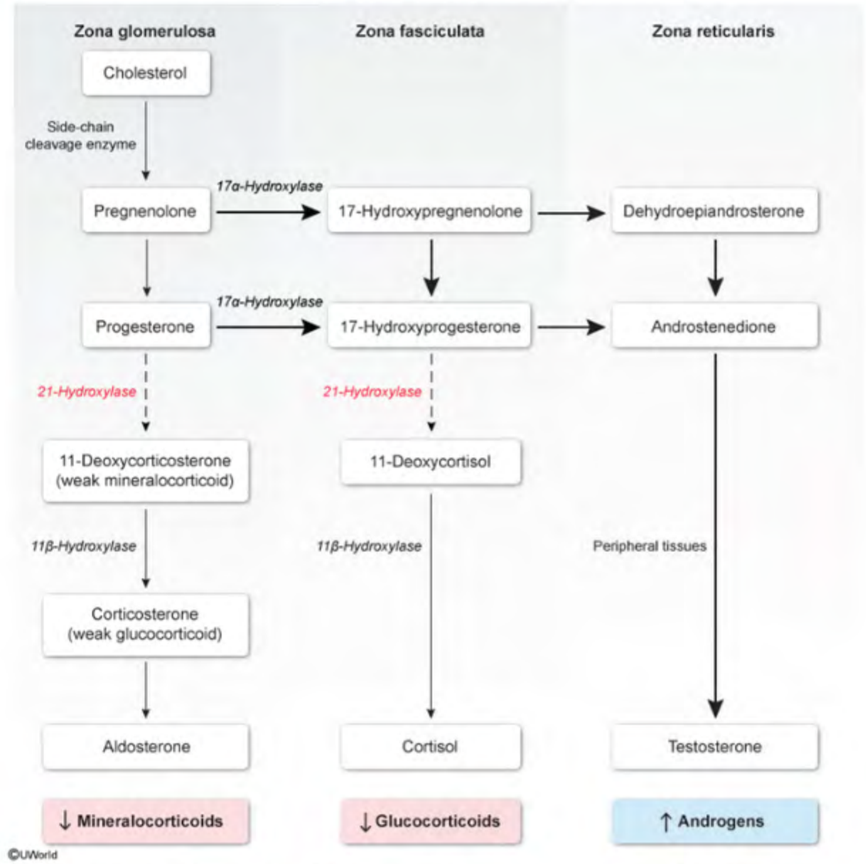
2023 Version

Explanation

https://t.me/USMLEWorldStep1

C. ↓ ↓ ↑ ↓ (16%)

Exhibit Display



Zoom In Zoom Out Reset New | Existing My Notebook

Corticosterone

https://t.me/USMLEWorldStep1

This infant is dehydrated (ie, sunken fontanelle, dry mucous membranes) with hypotension, hyponatremia, and hyperkalemia. These findings are consistent with classic **congenital adrenal hyperplasia** (CAH) due to **21-hydroxylase deficiency**.

Patients with 21-hydroxylase deficiency cannot convert 17-hydroxyprogesterone (17-OHP) into 11-deoxycortisol, which results in **elevated 17-OHP** and **decreased aldosterone and cortisol** production. Corticosteroid precursors accumulate and are diverted toward **excess adrenal androgen** biosynthesis. Low cortisol levels (ie, loss of negative feedback) also trigger **increased ACTH** production by the anterior pituitary, which further stimulates the formation of adrenal androgens **(Choice D)**.

Although affected girls are usually identified at birth due to ambiguous genitalia (virilization) from excess androgens, boys have normal genitalia and typically are identified at age 1-2 weeks with vomiting, **hypotension**, **hyponatremia**, and **hyperkalemia** due to lack of sufficient mineralocorticoids **(salt wasting)**. Cortisol deficiency causes hypoglycemia and further impairs the ability to maintain blood pressure.

(Choice B) CAH due to 17 alpha-hydroxylase deficiency prevents the conversion of progesterone to 17-OHP, resulting in low 17-OHP, cortisol, and adrenal androgen production. In contrast to this case, hypertension and hypokalemia occur with 17 alpha-hydroxylase deficiency due to increased mineralocorticoids.

(Choice C) Adrenal steroid synthesis is also impaired with primary adrenal insufficiency (ie, Addison disease); however, autoimmune destruction of the adrenal glands is unlikely to occur in the first week of life, making 21-hydroxylase deficiency a much more likely cause of adrenal crisis in this patient.

(Choice E) An ACTH-secreting tumor causes increased synthesis of cortisol and its precursors (eg, 17-OHP). Cushing disease is rare in newborns and would be associated with glucocorticoid-induced hypertension (not hypotension) and subsequent inhibition of aldosterone.

Educational objective:
Classic 21-hydroxylase deficiency causes decreased cortisol and aldosterone production with increased adrenal androgen production. In boys, this deficiency presents 1-2 weeks after birth with vomiting, hypotension, hyponatremia, and hyperkalemia due to salt wasting; genitalia are normal. In girls, it presents at birth with ambiguous genitalia.

https://t.me/USMLEWorldStep1

This infant is dehydrated (ie, sunken fontanelle, dry mucous membranes) with hypotension, hyponatremia, and hyperk

hydro

Patien
which
precur
loss of
stimula

Althou
androg

hypor
causes

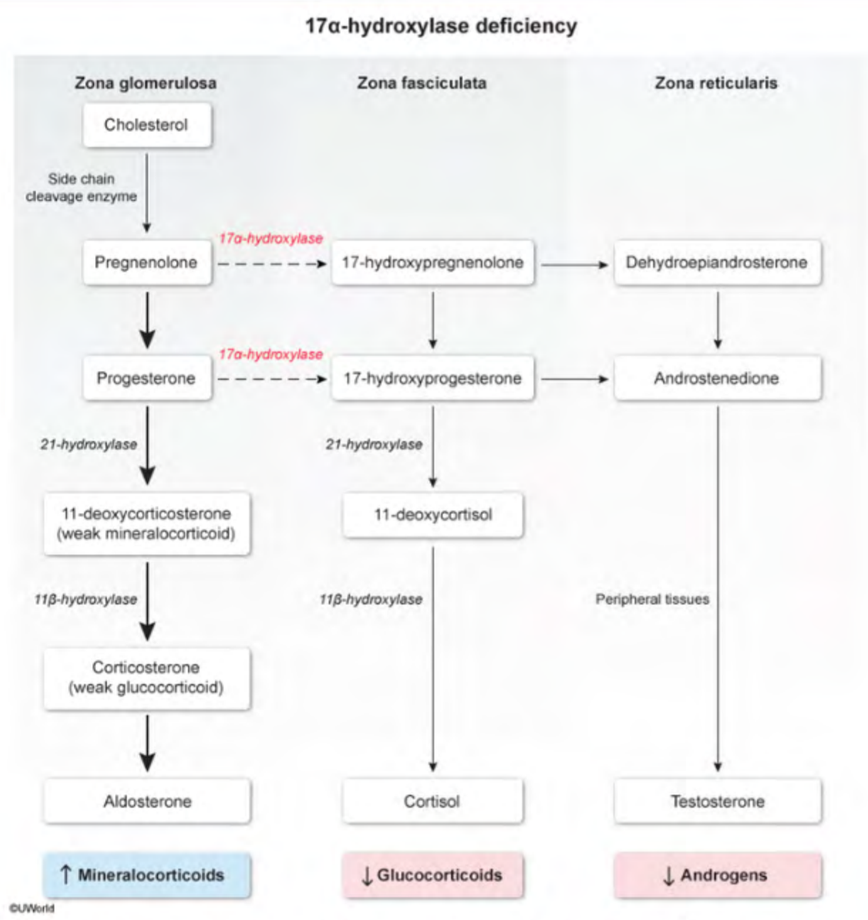
(Choi
resulti
hypok

(Choi
howev
hydrox

(Choi
Cushir
hypote

Educa
Classi
androg
hypon
ambiguous genitalia.

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

A 13-year-old boy is brought to the clinic due to progressive difficulty with breathing, hoarseness, and dysphagia. The symptoms began insidiously 6 months ago but have rapidly become worse in the last 4 weeks. The patient has no associated skin rash, pharyngeal pain, fever, weight loss, or loss of appetite. Medical history is unremarkable and the patient takes no medications. He is up to date on scheduled vaccinations. The patient's parents and siblings have no history of significant health problems. Vital signs are normal, and he is at 70th percentile for height and weight. Oropharyngeal examination reveals a large, red lingual mass. The patient subsequently undergoes excision of the mass; histopathologic preparation of the recovered tissue is shown in the image below.

Failure of which of the following embryologic processes is most likely responsible for this patient's lesion?

- A. Apoptosis
- B. Differentiation
- C. Fusion
- D. Migration
- E. Proliferation

Submit

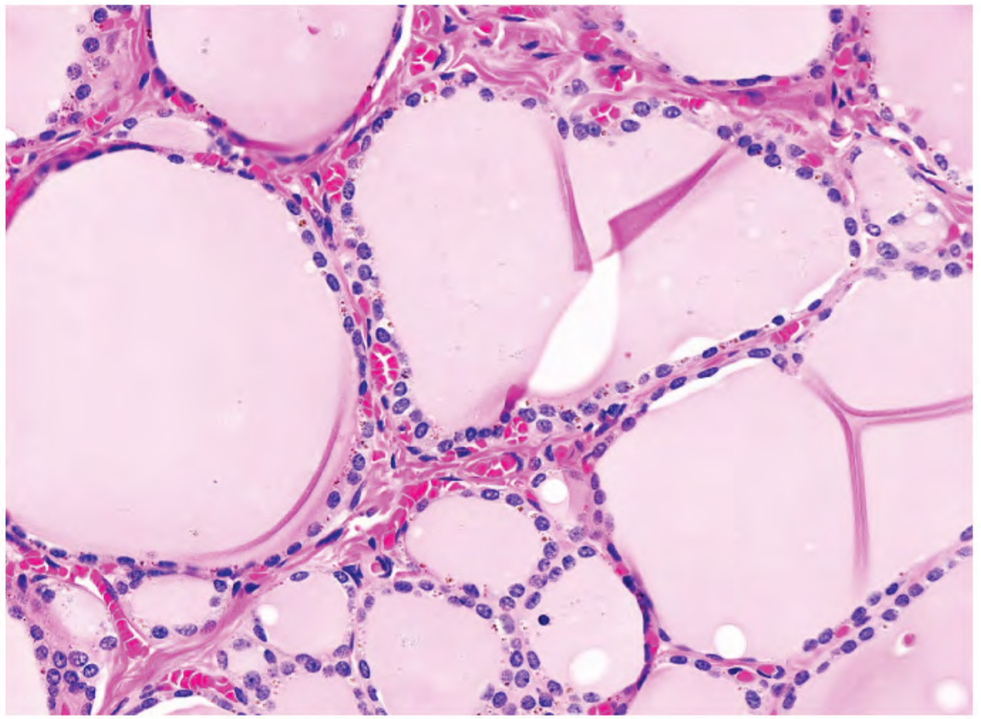
https://t.me/USMLEWorldStep1

A 13-year-old boy is brought to the clinic due to progressive difficulty with breathing, hoarseness, and dysphagia.
The sy
has nc
unrem
parent
percer
subse
image

Failure

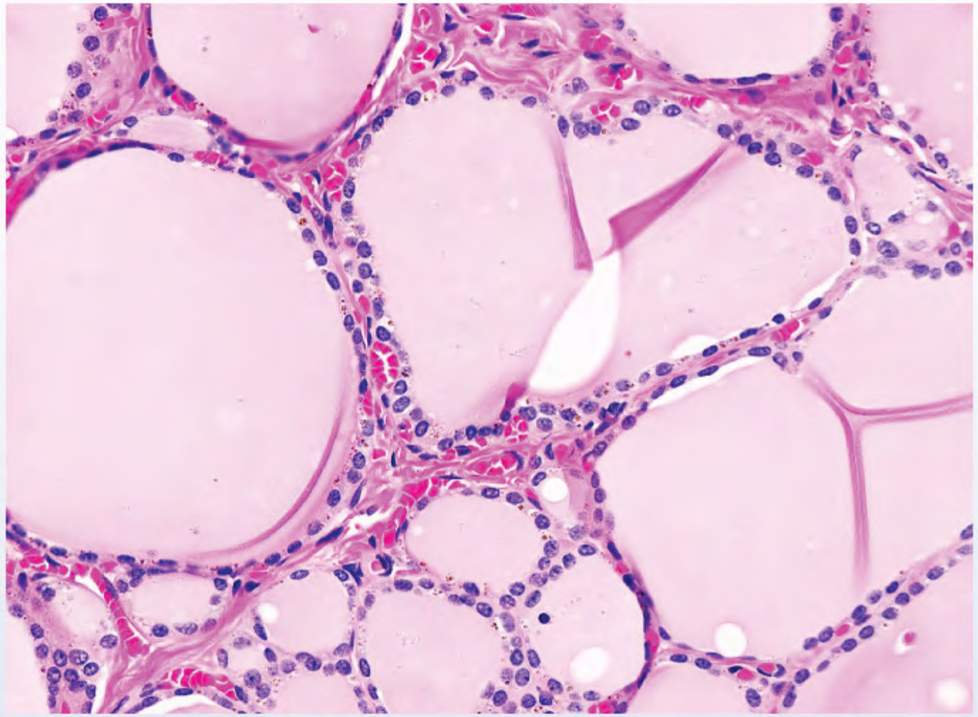
A. Apoptosis

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

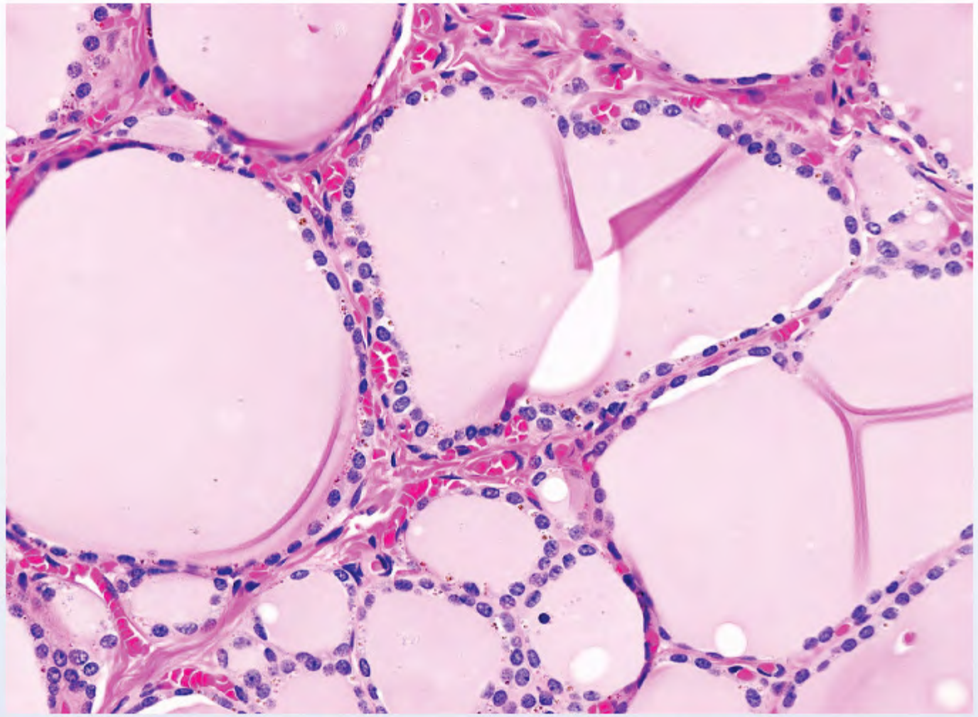


Failure of which of the following embryologic processes is most likely responsible for this patient's lesion?

- A. Apoptosis
- B. Differentiation
- C. Fusion
- D. Migration
- E. Proliferation

Submit

https://t.me/USMLEWorldStep1



Failure of which of the following embryologic processes is most likely responsible for this patient's lesion?

- A. Apoptosis (14%)
- B. Differentiation (3%)
- ✗ C. Fusion (2%)
- ✓ D. Migration (76%)
- E. Proliferation (3%)

Incorrect
Correct answer
D

76%
Answered correctly

15 secs
Time Spent

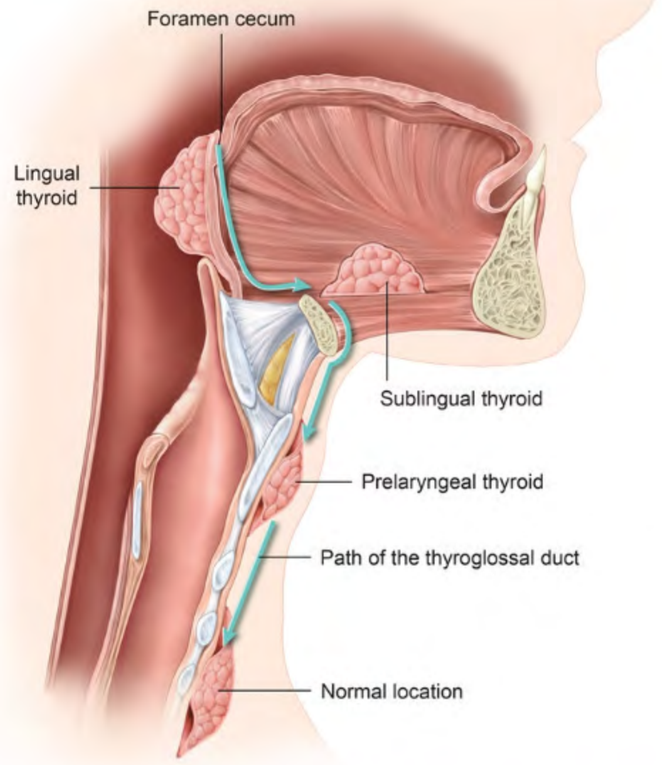
2023
Version

https://t.me/USMLEWorldStep1

B. Differentiation (3%)

Exhibit Display

Thyroid migration



©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Sublingual thyroid

https://t.me/USMLEWorldStep1

©UWorld

This patient's pathologic specimen shows normal thyroid follicles containing colloid, consistent with a **lingual thyroid**. The thyroid gland is formed from an outpouching (evagination) of the pharyngeal epithelium and subsequently descends to the lower neck anterior to the upper trachea and larynx. The lowest part of the evagination forms the thyroid gland and the remaining portion forms the **thyroglossal duct**, which extends from the foramen cecum on the dorsal surface of the tongue to the superior border of the thyroid isthmus.

Due to **failure of migration**, the thyroid can reside anywhere along the thyroglossal duct's usual path, including the tongue (lingual thyroid). Enlargement of a lingual thyroid can lead to **obstructive symptoms** (eg, dysphagia, dysphonia, dyspnea), typically during times of heightened thyroid stimulation (eg, puberty, pregnancy). Sometimes, this lingual thyroid is the only thyroid tissue in the body, so hypothyroidism can occur if it is removed.

(Choice A) Apoptosis is the process of programmed cell death and is important in regulating the turnover of cells. Failure of apoptosis during fetal development can result in conditions such as duodenal atresia and syndactyly (ie, fusion of adjacent digits).

(Choice B) Differentiation is the formation of mature cells from undifferentiated precursor cells (eg, formation of red blood cells, white blood cells, and platelets from bone marrow stem cells). Although thyroid cells do differentiate after their descent from the pharynx, defective differentiation would result in impaired thyroid follicle formation.

(Choice C) Fusion is the joining of two opposing tissues to form one continuous structure. Disruption of this process leads to a variety of birth defects, including cleft palate, atrioventricular septal defects, pancreatic divisum, and neural tube defects.

(Choice E) Proliferation denotes an increase in the number of cells via mitosis. Failure of proliferation during fetal development can result in organ hypoplasia (eg, thymus abnormalities in DiGeorge syndrome).

Educational objective:
The thyroid gland is formed from evagination of the pharyngeal epithelium and descends to the lower neck. Due to failure of migration, the thyroid can reside anywhere along the thyroglossal duct's usual path, including the tongue (lingual thyroid).

https://t.me/USMLEWorldStep1

©UWorld

This p
thyroi
subse
evagin
the for

Due to
the tor
dysph
Somet

(Choi
Failure
fusion

(Choi
red blo
differe
format

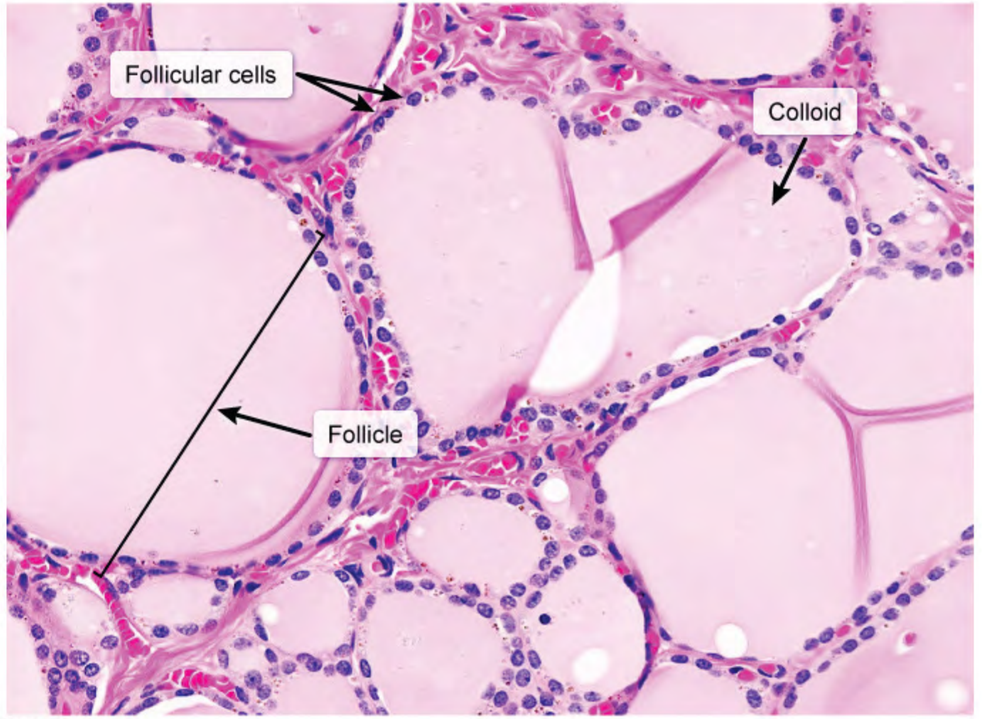
(Choi
proces
and ne

(Choi
develo

Educa
The th
failure
(lingual thyroid).

Exhibit Display

Normal thyroid gland



©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

A 46-year-old woman comes to the office for follow-up. Six months ago, the patient underwent total thyroidectomy followed by radioactive iodine ablation for invasive follicular thyroid cancer with distant metastasis. After surgery, she was prescribed levothyroxine to prevent thyroid cancer regrowth. Over the past 4 months, the patient has had a 4.5-kg (10 lb) unintentional weight loss despite having a normal appetite. She also feels unusually hot and sweaty. Temperature is 37 C (98.6 F), blood pressure is 150/70 mm Hg, pulse is 110/min, and respirations are 17/min. Examination reveals a fine hand tremor and sweaty palms. Serum thyroid function testing would most likely reveal which of the following?

	TSH	Thyroxine (T4)	Triiodothyronine (T3)
○ A.	Decreased	Increased	Increased
○ B.	Decreased	Decreased	Increased
○ C.	Decreased	Normal	Normal
○ D.	Decreased	Normal	Decreased
○ E.	Increased	Increased	Increased
○ F.	Decreased	Increased	Decreased

Submit

https://t.me/USMLEWorldStep1

A 46-year-old woman comes to the office for follow-up. Six months ago, the patient underwent total thyroidectomy followed by radioactive iodine ablation for invasive follicular thyroid cancer with distant metastasis. After surgery, she was prescribed levothyroxine to prevent thyroid cancer regrowth. Over the past 4 months, the patient has had a 4.5-kg (10 lb) unintentional weight loss despite having a normal appetite. She also feels unusually hot and sweaty. Temperature is 37 C (98.6 F), blood pressure is 150/70 mm Hg, pulse is 110/min, and respirations are 17/min. Examination reveals a fine hand tremor and sweaty palms. Serum thyroid function testing would most likely reveal which of the following?

		TSH	Thyroxine (T4)	Triiodothyronine (T3)	
✓	A.	Decreased	Increased	Increased	(74%)
	B.	Decreased	Decreased	Increased	(10%)
	C.	Decreased	Normal	Normal	(1%)
	D.	Decreased	Normal	Decreased	(0%)
	E.	Increased	Increased	Increased	(2%)
	F.	Decreased	Increased	Decreased	(10%)

Correct

74%
Answered correctly

04 secs
Time Spent

2023
Version

Explanation

Exogenous thyrotoxicosis	
	• Thyroid replacement dosing error • Levothyroxine suppression of thyroid cancer

https://t.me/USMLEWorldStep1

Explanation

Exogenous thyrotoxicosis	
Causes	• Thyroid replacement dosing error • Levothyroxine suppression of thyroid cancer • Nonprescribed thyroid hormone use (eg, factitious disorder, weight loss supplements)
Laboratory markers	• Elevated T3 and thyroxine levels* • Suppressed TSH • Low serum thyroglobulin • Low radioiodine uptake
*Use of T3 supplement (liothyronine) shows elevated T3 only. **T3** = triiodothyronine.	

This patient has **thyrotoxicosis** (eg, weight loss, tremor, tachycardia) due to suppressive-dose levothyroxine therapy. Because TSH can promote growth of residual malignant cells following thyroidectomy, patients with **thyroid cancer** at high risk of recurrence (eg, known metastasis) are often prescribed **levothyroxine** doses that are **higher** than what is needed for simple replacement. These higher doses adequately **suppress pituitary secretion of TSH**, however, they can also cause symptomatic thyrotoxicosis.

When exogenous thyrotoxicosis is due to levothyroxine or mixed T3/T4 supplements (eg, porcine thyroid extract), **total and free thyroxine (T4) levels are elevated**; triiodothyronine (T3) is produced primarily by deiodination of T4 in peripheral tissues, so **T3 levels also are elevated**, even if the patient is taking levothyroxine only **(Choice F)**. In contrast, thyrotoxicosis due to the intake of liothyronine (exogenous T3) is associated with high serum T3 and low T4 **(Choice B)**.

(Choice C) Subclinical hyperthyroidism is characterized by a mildly suppressed TSH with normal thyroid hormone levels. Patients with subclinical hyperthyroidism are typically asymptomatic. This patient takes suppressive-dose levothyroxine to manage metastatic thyroid cancer and has overt hyperthyroid symptoms; thyroid hormone levels

https://t.me/USMLEWorldStep1

T3 = triiodothyronine.

This patient has **thyrotoxicosis** (eg, weight loss, tremor, tachycardia) due to suppressive-dose levothyroxine therapy. Because TSH can promote growth of residual malignant cells following thyroidectomy, patients with **thyroid cancer** at high risk of recurrence (eg, known metastasis) are often prescribed **levothyroxine** doses that are **higher** than what is needed for simple replacement. These higher doses adequately **suppress pituitary secretion of TSH**, however, they can also cause symptomatic thyrotoxicosis.

When exogenous thyrotoxicosis is due to levothyroxine or mixed T3/T4 supplements (eg, porcine thyroid extract), **total and free thyroxine (T4) levels are elevated**; triiodothyronine (T3) is produced primarily by deiodination of T4 in peripheral tissues, so **T3 levels also are elevated**, even if the patient is taking levothyroxine only **(Choice F)**. In contrast, thyrotoxicosis due to the intake of liothyronine (exogenous T3) is associated with high serum T3 and low T4 **(Choice B)**.

(Choice C) Subclinical hyperthyroidism is characterized by a mildly suppressed TSH with normal thyroid hormone levels. Patients with subclinical hyperthyroidism are typically asymptomatic. This patient takes suppressive-dose levothyroxine to manage metastatic thyroid cancer and has overt hyperthyroid symptoms; thyroid hormone levels are likely to be elevated.

(Choice D) Patients with severe, acute illness may develop thyroid function abnormalities resembling a mild central hypothyroid state, with low TSH, normal T4, and low T3 (ie, euthyroid sick syndrome). Patients receiving suppressive-dose levothyroxine typically have normal or elevated T3 due to peripheral deiodination.

(Choice E) Central/secondary hyperthyroidism (eg, TSH-secreting pituitary adenoma) is characterized by elevated TSH and thyroid hormone levels. Patients receiving suppressive-dose levothyroxine have low TSH due to feedback inhibition of TSH release.

Educational objective:
Exogenous thyrotoxicosis can be caused by suppressive levothyroxine therapy for thyroid cancer. When exogenous thyrotoxicosis is due to levothyroxine or mixed T3/T4 supplements, thyroxine (T4) levels are elevated; triiodothyronine (T3) is produced primarily by the peripheral deiodination of T4, so T3 levels also are elevated even if the patient is taking T4 only.

https://t.me/USMLEWorldStep1

T3 = triiodothyronine.

This p
therap
thyroi
are **hi**
secret

When
total a
in peri
contra
T4 **(CH**

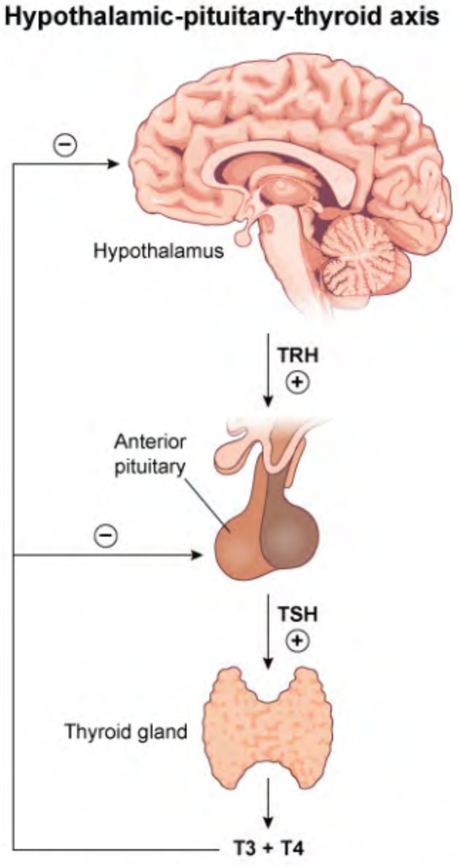
(Choi
levels.
levoth
are lik

(Choi
centra
suppre

(Choi
TSH a
feedba

Educa
Exoge
exoge
triiodo
if the patient is taking T4 only.

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

A 26-year-old pregnant woman at 16 weeks gestation comes to the office for prenatal follow-up. The patient has a 2-year history of mild hyperthyroidism due to Graves disease and started taking propylthiouracil when she decided to attempt pregnancy. The patient has had no tremulousness, palpitations, diarrhea, or heat intolerance. She has no other medical problems and no drug allergies. She takes a prenatal vitamin. The patient does not use tobacco, alcohol, or illicit drugs. Temperature is 36.7 C (98 F), blood pressure is 110/60 mm Hg, and pulse is 88/min. Physical examination reveals no lid lag, exophthalmos, or hand tremors. The thyroid gland is normal to palpation. Fetal heart rate is normal. Thyroid hormone levels are within the laboratory's reference ranges. During this visit, her thyroid treatment is changed from propylthiouracil to methimazole. Switching the patient's therapy at this time is aimed at decreasing which of the following complications?

- A. Fetal skin abnormalities
- B. Fetal thyroid agenesis
- C. Maternal hepatotoxicity
- D. Maternal ophthalmopathy
- E. Maternal thyroid cancer

Submit

https://t.me/USMLEWorldStep1

A 26-year-old pregnant woman at 16 weeks gestation comes to the office for prenatal follow-up. The patient has a 2-year history of mild hyperthyroidism due to Graves disease and started taking propylthiouracil when she decided to attempt pregnancy. The patient has had no tremulousness, palpitations, diarrhea, or heat intolerance. She has no other medical problems and no drug allergies. She takes a prenatal vitamin. The patient does not use tobacco, alcohol, or illicit drugs. Temperature is 36.7 C (98 F), blood pressure is 110/60 mm Hg, and pulse is 88/min. Physical examination reveals no lid lag, exophthalmos, or hand tremors. The thyroid gland is normal to palpation. Fetal heart rate is normal. Thyroid hormone levels are within the laboratory's reference ranges. During this visit, her thyroid treatment is changed from propylthiouracil to methimazole. Switching the patient's therapy at this time is aimed at decreasing which of the following complications?

- ✗ A. Fetal skin abnormalities (16%)
- B. Fetal thyroid agenesis (38%)
- ✓ C. Maternal hepatotoxicity (43%)
- D. Maternal ophthalmopathy (0%)
- E. Maternal thyroid cancer (0%)

Incorrect
Correct answer
C

43%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

Thionamide **antithyroid drugs** (eg, propylthiouracil [PTU], methimazole) are used to decrease thyroid hormone production. In Graves disease, they can be used to induce a euthyroid state in preparation for definitive treatment with radioiodine or surgery and can sometimes achieve remission in patients with mild disease.

Methimazole is preferred for most patients due the **hepatotoxicity** of PTU; PTU often causes transient elevations in hepatic transaminases and occasionally can cause severe idiosyncratic liver injury with acute liver failure.

https://t.me/USMLEWorldStep1

Explanation

Thionamide **antithyroid drugs** (eg, propylthiouracil [PTU], methimazole) are used to decrease thyroid hormone production. In Graves disease, they can be used to induce a euthyroid state in preparation for definitive treatment with radioiodine or surgery and can sometimes achieve remission in patients with mild disease.

Methimazole is preferred for most patients due the **hepatotoxicity** of PTU; PTU often causes transient elevations in hepatic transaminases and occasionally can cause severe idiosyncratic liver injury with acute liver failure. However, **methimazole** has potential **teratogenic effects** (eg, aplasia cutis **[Choice A]**, esophageal atresia, facial anomalies), so PTU is preferred in the first trimester of pregnancy. Thereafter, the patient should be returned to methimazole therapy.

(Choice B) Thyroid dysgenesis (abnormal development of the thyroid gland) can manifest as absence (agenesis), ectopic location, or hypoplasia of the thyroid gland. The thyroid gland is normally fully developed by week 12; therefore, switching from PTU to methimazole at 16 weeks gestation is unlikely to cause thyroid dysgnesis. Thionamide antithyroid drugs can cause hypothyroidism with goiter (rather than dysgenesis) in newborns, but the effects are typically transient as the drugs are cleared within days.

(Choice D) Graves ophthalmopathy is due to the activation of TSH receptors on orbital fibroblasts by thyrotropin receptor autoantibodies, which leads to the expansion of the ground substance of retro-orbital tissues and edema of the extraocular muscles. Radioiodine therapy for Graves disease can acutely worsen ophthalmopathy, but this is less of a concern with antithyroid drugs.

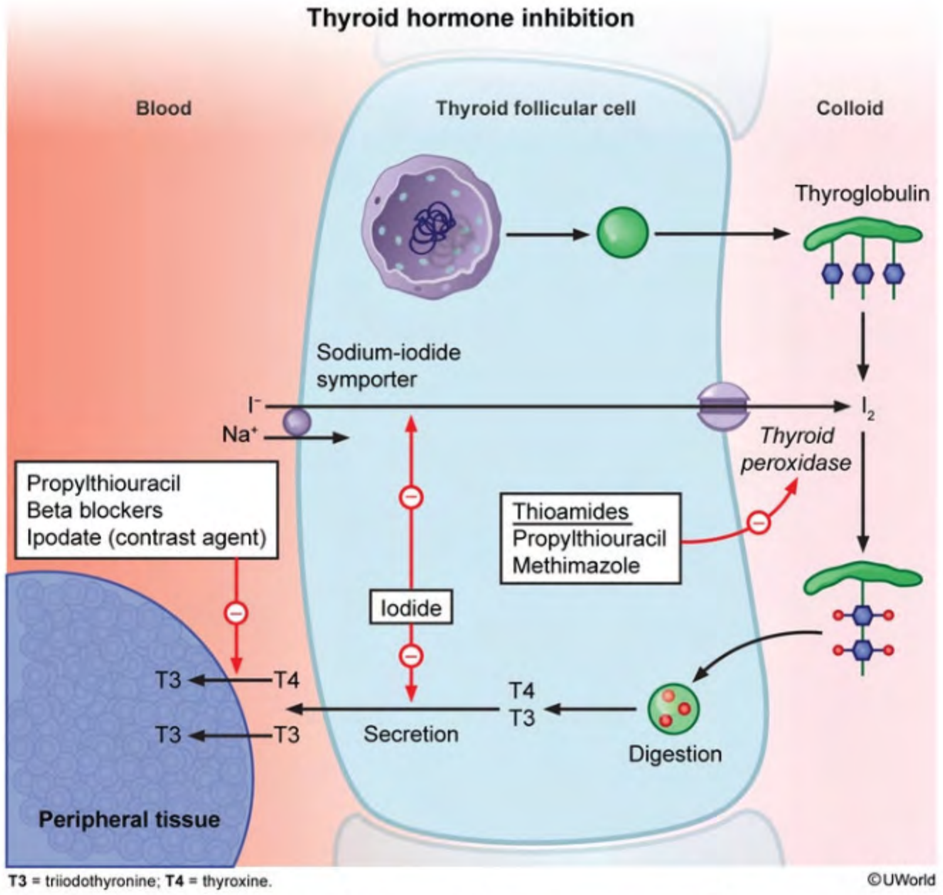
(Choice E) Risk factors for thyroid cancer include exposure to ionizing radiation, iodine-deficient diet, and certain familial cancer syndromes (eg, familial adenomatous polyposis). Antithyroid drugs do not increase the risk for thyroid cancer.

Educational objective:
Thionamide antithyroid drugs (eg, propylthiouracil [PTU], methimazole) are used to decrease thyroid hormone production. Methimazole is preferred for most patients due to the hepatotoxicity of PTU. However, methimazole has potential teratogenic effects, so PTU is preferred in the first trimester of pregnancy.

https://t.me/USMLEWorldStep1

Explanation

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Thiona
produ
with ra

Methir
in hep
Howev
anoma
methir

(Choi
ectopi
therefo
Thiona
effects

(Choi
recept
of the
is less

(Choi
familia
thyroid

Educa
Thiona
produ
has potential teratogenic effects, so PTU is preferred in the first trimester of pregnancy.

https://t.me/USMLEWorldStep1

A 20-year-old woman comes to the emergency department with lethargy, abdominal pain, and nausea. She has had polyuria and excessive thirst for one day. She also complains of dysuria and chills over the last few days but did not seek medical care until today. Physical examination shows tachycardia and dry mucous membranes. Laboratory results are as follows:

Serum chemistry panel

Sodium	130 mEq/L
Chloride	93 mEq/L
Bicarbonate	12 mEq/L
Blood urea nitrogen	30 mg/dL
Creatinine	1.3 mg/dL
Calcium	10.0 mg/dL
Glucose	698 mg/dL

Which of the following electrolyte findings would most likely be seen in this patient?

	Extracellular potassium concentration	Intracellular potassium stores
○ A.	Decreased	Decreased
○ B.	Decreased	Increased
○ C.	Increased	Decreased
○ D.	Increased	Increased
○ E.	No Change	No change

Submit

https://t.me/USMLEWorldStep1

A 20-year-old woman comes to the emergency department with lethargy, abdominal pain, and nausea. She has had polyuria and excessive thirst for one day. She also complains of dysuria and chills over the last few days but did not seek medical care until today. Physical examination shows tachycardia and dry mucous membranes. Laboratory results are as follows:

Serum chemistry panel

Sodium	130 mEq/L
Chloride	93 mEq/L
Bicarbonate	12 mEq/L
Blood urea nitrogen	30 mg/dL
Creatinine	1.3 mg/dL
Calcium	10.0 mg/dL
Glucose	698 mg/dL

Which of the following electrolyte findings would most likely be seen in this patient?

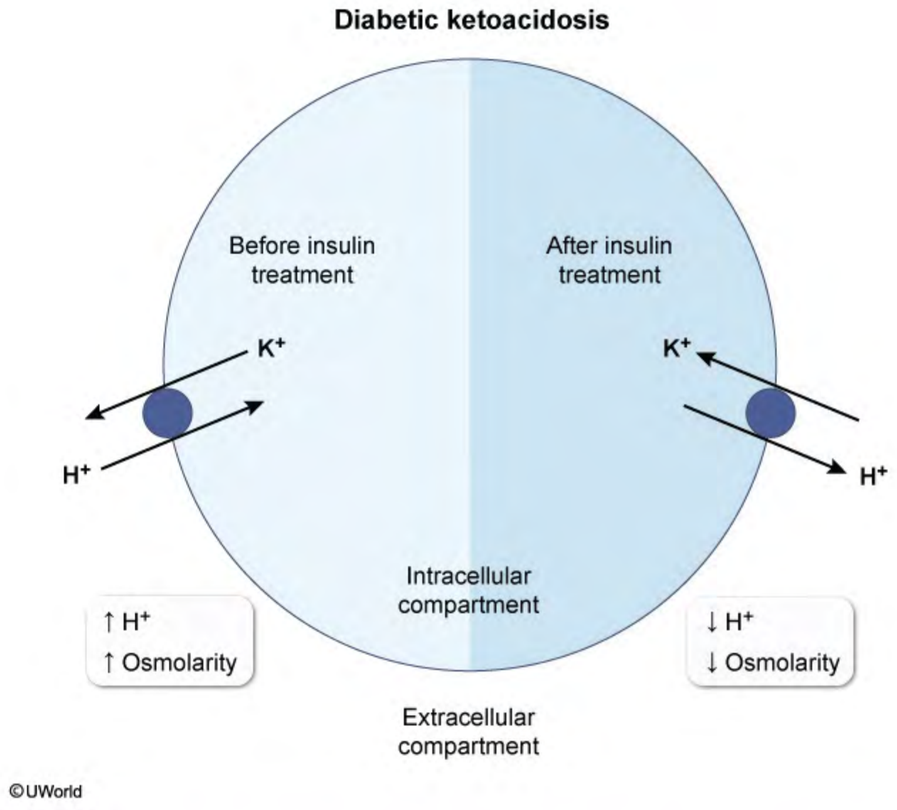
	Extracellular potassium concentration	Intracellular potassium stores	
✗ ◉	A. Decreased	Decreased	(6%)
○	B. Decreased	Increased	(12%)
✓ ○	C. Increased	Decreased	(77%)
○	D. Increased	Increased	(2%)
○	E. No Change	No change	(0%)

Incorrect

https://t.me/USMLEWorldStep1

C. Increased — Decreased — (77%)

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Extracellular compartment

https://t.me/USMLEWorldStep1

This young patient has both clinical (eg, polyuria, polydipsia, volume depletion) and biochemical (eg, hyperglycemia, low bicarbonate, high anion gap, decreased serum sodium levels) signs of diabetic ketoacidosis (DKA). DKA is often precipitated by infections, including urinary tract infections (likely in this patient). Patients with DKA lose significant amounts of potassium in the urine, primarily via glycosuria-induced osmotic diuresis and hypovolemia-mediated increase in aldosterone secretion. This results in a **total body potassium deficit** that is reflected by decreased intracellular potassium stores (since 98% of the body's potassium is stored intracellularly). Despite the low intracellular potassium levels, **extracellular potassium concentrations are normal or increased** due to the following mechanisms:

1. Loss of intracellular free water caused by increased plasma osmolality leads to extracellular movement of potassium secondary to increasing intracellular potassium concentration
2. Lack of insulin also causes extracellular shifting of potassium as insulin normally promotes cellular uptake of potassium

Clinicians must be careful when giving insulin and intravenous fluids during resuscitation of dehydrated, hyperglycemic patients. These interventions force potassium back into the cells, causing a precipitous drop in serum potassium due to the total body deficit. Despite normal or elevated serum potassium, timely administration of potassium supplementation is essential when treating a patient with DKA.

(Choice A) A decrease in both intra- and extracellular potassium levels is seen with mineralocorticoids excess, diuretic use, and chronic gastrointestinal losses.

(Choice B) Extracellular potassium concentration decreases following glucose and insulin administration as potassium moves into the intracellular compartment. Stimulation of beta-adrenergic receptors also causes increased transfer of potassium to the intracellular compartment.

(Choice D) Renal excretion of potassium is impaired in most patients with chronic renal failure, resulting in increased total body potassium storage and hyperkalemia.

(Choice E) Normal extracellular potassium levels are common in patients with DKA as the extracellular potassium shift is often mitigated by increased urinary potassium losses. However, intracellular potassium levels are always decreased in DKA.

https://t.me/USMLEWorldStep1

Despite the low intracellular potassium levels, **extracellular potassium concentrations are normal or increased** due to the following mechanisms:

1. Loss of intracellular free water caused by increased plasma osmolality leads to extracellular movement of potassium secondary to increasing intracellular potassium concentration
2. Lack of insulin also causes extracellular shifting of potassium as insulin normally promotes cellular uptake of potassium

Clinicians must be careful when giving insulin and intravenous fluids during resuscitation of dehydrated, hyperglycemic patients. These interventions force potassium back into the cells, causing a precipitous drop in serum potassium due to the total body deficit. Despite normal or elevated serum potassium, timely administration of potassium supplementation is essential when treating a patient with DKA.

(Choice A) A decrease in both intra- and extracellular potassium levels is seen with mineralocorticoids excess, diuretic use, and chronic gastrointestinal losses.

(Choice B) Extracellular potassium concentration decreases following glucose and insulin administration as potassium moves into the intracellular compartment. Stimulation of beta-adrenergic receptors also causes increased transfer of potassium to the intracellular compartment.

(Choice D) Renal excretion of potassium is impaired in most patients with chronic renal failure, resulting in increased total body potassium storage and hyperkalemia.

(Choice E) Normal extracellular potassium levels are common in patients with DKA as the extracellular potassium shift is often mitigated by increased urinary potassium losses. However, intracellular potassium levels are always decreased in DKA.

Educational objective:
Most patients with diabetic ketoacidosis have normal to increased serum potassium levels despite a total body potassium deficit. Replacement of potassium is a crucial step in the management of patients with diabetic ketoacidosis.

Pathophysiology	Endocrine, Diabetes & Metabolism	Diabetic ketoacidosis
Subject	System	Topic

https://t.me/USMLEWorldStep1

A 22-year-old man comes to the emergency department with abdominal pain and vomiting. His symptoms began acutely 24 hours ago with nausea and decreased appetite. His medical history is unremarkable. The patient drinks 3-4 beers a week and does not use tobacco or illicit drugs. BMI is 37 kg/m^2. Physical examination is notable for moderate epigastric tenderness with decreased bowel sounds but no rebound tenderness, guarding, or abdominal rigidity. Fasting laboratory studies show a serum triglyceride concentration of 1,500 mg/dL (normal: <200 mg/dL). Once the patient has been medically stabilized, which of the following medications would be most helpful in preventing recurrences of his condition?

- A. Atorvastatin
- B. Cholestyramine
- C. Ezetimibe
- D. Fenofibrate
- E. Niacin
- F. Omega-3 fatty acids

Submit

https://t.me/USMLEWorldStep1

A 22-year-old man comes to the emergency department with abdominal pain and vomiting. His symptoms began acutely 24 hours ago with nausea and decreased appetite. His medical history is unremarkable. The patient drinks 3-4 beers a week and does not use tobacco or illicit drugs. BMI is 37 kg/m^2. Physical examination is notable for moderate epigastric tenderness with decreased bowel sounds but no rebound tenderness, guarding, or abdominal rigidity. Fasting laboratory studies show a serum triglyceride concentration of 1,500 mg/dL (normal: <200 mg/dL). Once the patient has been medically stabilized, which of the following medications would be most helpful in preventing recurrences of his condition?

- ✗ A. Atorvastatin (14%)
- B. Cholestyramine (7%)
- C. Ezetimibe (6%)
- ✓ D. Fenofibrate (59%)
- E. Niacin (11%)
- F. Omega-3 fatty acids (1%)

Incorrect
Correct answer
D

59%
Answered correctly

04 secs
Time Spent

2023
Version

Explanation

Antihyperlipidemic medications

Drug	Mechanism	Major lipid effects	Adverse effects
Statins	• Inhibit HMG-CoA reductase	• ↓↓ LDL • ↓ Triglycerides	• Hepatotoxicity • Muscle toxicity

https://t.me/USMLEWorldStep1

Explanation

Antihyperlipidemic medications			
Drug	**Mechanism**	**Major lipid effects**	**Adverse effects**
Statins	• Inhibit HMG-CoA reductase	• ↓↓ LDL • ↓ Triglycerides	• Hepatotoxicity • Muscle toxicity
Ezetimibe	• ↓ Intestinal cholesterol absorption	• ↓ LDL	• ↑ Hepatotoxicity if given with statins
Bile acid sequestrants	• Prevent reabsorption of bile acids in the intestine	• ↓ LDL	• Nausea, bloating, cramping • Impaired drug & fat-soluble vitamin absorption
Niacin	• ↓ Fatty acid release • ↓ VLDL synthesis • ↓ HDL clearance	• ↓ LDL • ↑↑ HDL	• Flushing & pruritus • Hepatotoxicity • Hyperuricemia/gout
Fibrates	• Activate PPAR-α • ↓ VLDL synthesis	• ↓↓ Triglycerides • ↑ HDL	• Muscle toxicity • Gallstones
Fish oil/ omega-3 fatty acids	• ↓ VLDL synthesis • ↓ Apolipoprotein B synthesis	• ↓ Triglycerides • ↑ HDL	• Fishy taste
PPAR-α = peroxisome proliferator-activated receptor-alpha.			

This patient most likely has **acute pancreatitis** due to severe **hypertriglyceridemia**. Small quantities of pancreatic lipase normally leak into the pancreatic capillaries, where they can metabolize triglycerides to **free fatty acids**, which have toxic and inflammatory effects on the pancreas. The risk of pancreatitis rises with increasing

https://t.me/USMLEWorldStep1

PPAR-α = peroxisome proliferator-activated receptor-alpha.

This patient most likely has **acute pancreatitis** due to severe **hypertriglyceridemia**. Small quantities of pancreatic lipase normally leak into the pancreatic capillaries, where they can metabolize triglycerides to **free fatty acids**, which have toxic and inflammatory effects on the pancreas. The risk of pancreatitis rises with increasing triglyceride levels and is most significant when triglycerides are severely elevated (>1,000 mg/dL).

Triglycerides loosely reflect caloric balance; a calorie-restricted diet with increased exercise and reduced alcohol intake can provide a rapid and significant drop in triglyceride levels. Lipid-lowering medications are also indicated for patients with moderate to severe hypertriglyceridemia. **Fibrates** (eg, fenofibrate, gemfibrozil) work by activating peroxisome proliferator-activated receptor-alpha (**PPAR-α**), which increases the synthesis of lipoprotein lipase.

(Choice A) Although statins (eg, atorvastatin) are the preferred lipid-lowering agents for the prevention of cardiovascular disease, they only modestly lower triglyceride levels and would be less effective than fibrates for preventing recurrent pancreatitis due to hypertriglyceridemia.

(Choices B and C) Bile acid-binding resins (eg, cholestyramine) work by binding bile acids in the gastrointestinal tract, subsequently interfering with enterohepatic bile acid circulation. Ezetimibe selectively inhibits intestinal cholesterol absorption. These medications are used primarily for the treatment of hypercholesterolemia.

(Choice E) Niacin decreases hepatic production of VLDLs and reduces triglyceride release from adipose tissue. It has a weaker effect in lowering triglycerides than fibrates and is associated with significant side effects, especially flushing.

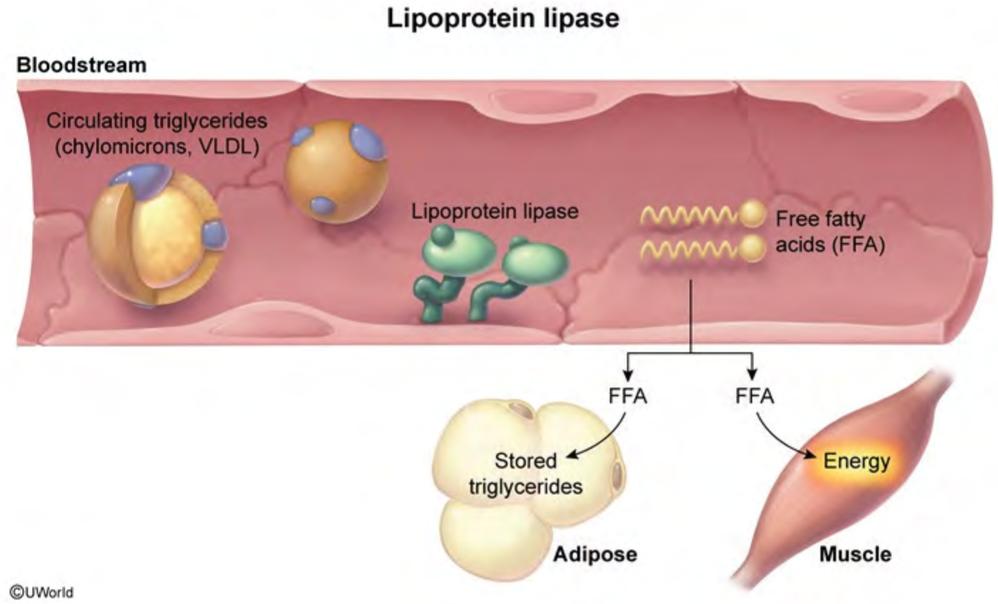
(Choice F) Fish oil supplements containing omega-3 fatty acids lower triglyceride levels by decreasing the production of VLDLs. Fish oils decrease serum triglycerides to a lesser degree than fibrates but may be added to fibrates in patients whose triglyceride levels are not adequately controlled with a fibrate alone.

Educational objective:
In patients with severe hypertriglyceridemia, pancreatic lipases can cause toxic levels of free fatty acids to be released within the pancreatic tissue, leading to acute pancreatitis. Fibrates (eg, fenofibrate) are the most effective agents for the treatment of hypertriglyceridemia.

https://t.me/USMLEWorldStep1

PPAR-α = peroxisome proliferator-activated receptor-alpha.

Exhibit Display



Zoom In Zoom Out Reset New | Existing My Notebook

This p
pancre
acids,
triglyc

Triglyc
intake
for pat
peroxi

(Choi
cardio
prever

(Choi
tract, s
choles

(Choi
has a
flushin

(Choi
produc
fibrate

Educa
In pati
releas
agents for the treatment of hypertriglyceridemia.

https://t.me/USMLEWorldStep1

A 15-year-old boy comes to the office for evaluation of a neck mass. The patient first noticed the mass a month ago and it has progressively enlarged. He has had no neck pain, fever, or difficulty swallowing or breathing. Examination shows a firm, nontender mass affecting the left thyroid lobe. TSH is within normal limits. Ultrasonography reveals a hypoechoic 2-cm nodule in the upper portion of the left thyroid lobe. Fine-needle biopsy reveals a cluster of large cells with abundant cytoplasm that stain positive for calcitonin. The patient is also found to be positive for a germline *RET* mutation. A total thyroidectomy is planned. Prior to the surgery, additional testing should be performed to evaluate for an abnormality in which of the following organs?

- A. Adrenal cortex
- B. Adrenal medulla
- C. Anterior pituitary
- D. Pancreatic islets
- E. Thymus

Submit

https://t.me/USMLEWorldStep1

A 15-year-old boy comes to the office for evaluation of a neck mass. The patient first noticed the mass a month ago and it has progressively enlarged. He has had no neck pain, fever, or difficulty swallowing or breathing. Examination shows a firm, nontender mass affecting the left thyroid lobe. TSH is within normal limits. Ultrasonography reveals a hypoechoic 2-cm nodule in the upper portion of the left thyroid lobe. Fine-needle biopsy reveals a cluster of large cells with abundant cytoplasm that stain positive for calcitonin. The patient is also found to be positive for a germline *RET* mutation. A total thyroidectomy is planned. Prior to the surgery, additional testing should be performed to evaluate for an abnormality in which of the following organs?

- ✗ A. Adrenal cortex (3%)
- ✓ B. Adrenal medulla (82%)
- C. Anterior pituitary (5%)
- D. Pancreatic islets (6%)
- E. Thymus (1%)

Incorrect
Correct answer
B

82%
Answered correctly

04 secs
Time Spent

2023
Version

Explanation

Multiple endocrine neoplasia type 2	
Inheritance	• Autosomal dominant • Germ-line activating mutations of *RET* proto-oncogene
Type 2A	• Medullary thyroid cancer (>95%) • Pheochromocytoma

https://t.me/USMLEWorldStep1

Multiple endocrine neoplasia type 2	
Inheritance	• Autosomal dominant • Germ-line activating mutations of *RET* proto-oncogene
Type 2A	• Medullary thyroid cancer (>95%) • Pheochromocytoma • Parathyroid hyperplasia
Type 2B	• Medullary thyroid cancer (>95%) • Pheochromocytoma • Mucosal neuromas, marfanoid habitus

This patient has **medullary thyroid cancer** (MTC), a neuroendocrine malignancy arising from the calcitonin-secreting parafollicular C cells. Most cases of MTC are sporadic, but approximately 20% are familial, due to germline mutations of the ***RET* proto-oncogene**. Multiple endocrine neoplasia type 2 (**MEN2**) is the most common inherited disorder associated with activating *RET* mutations, and is characterized by:

- MTC
- Pheochromocytoma
- Parathyroid hyperplasia (type 2A) or marfanoid habitus (tall, slender build, increased limb to height ratio) and mucosal neuromas (type 2B)

Pheochromocytoma is a catecholamine-secreting neoplasm arising from the chromaffin cells of the **adrenal medulla**. Up to 50% of patients with MEN2 develop pheochromocytoma. In patients with undiagnosed pheochromocytoma, induction of anesthesia can precipitate a catecholamine (epinephrine and norepinephrine) surge, leading to hypertensive crisis, flash pulmonary edema, and atrial fibrillation. Therefore, patients who have MTC associated with germline *RET* mutations should be screened for pheochromocytoma (eg, 24-hour assay for urinary metanephrines and catecholamines) prior to surgery.

https://t.me/USMLEWorldStep1

Type 2B	• Medullary thyroid cancer (>95%) • Pheochromocytoma • Mucosal neuromas, marfanoid habitus

This patient has **medullary thyroid cancer** (MTC), a neuroendocrine malignancy arising from the calcitonin-secreting parafollicular C cells. Most cases of MTC are sporadic, but approximately 20% are familial, due to germline mutations of the ***RET* proto-oncogene**. Multiple endocrine neoplasia type 2 (**MEN2**) is the most common inherited disorder associated with activating *RET* mutations, and is characterized by:

- MTC
- Pheochromocytoma
- Parathyroid hyperplasia (type 2A) or marfanoid habitus (tall, slender build, increased limb to height ratio) and mucosal neuromas (type 2B)

Pheochromocytoma is a catecholamine-secreting neoplasm arising from the chromaffin cells of the **adrenal medulla**. Up to 50% of patients with MEN2 develop pheochromocytoma. In patients with undiagnosed pheochromocytoma, induction of anesthesia can precipitate a catecholamine (epinephrine and norepinephrine) surge, leading to hypertensive crisis, flash pulmonary edema, and atrial fibrillation. Therefore, patients who have MTC associated with germline *RET* mutations should be screened for pheochromocytoma (eg, 24-hour assay for urinary metanephrines and catecholamines) prior to surgery.

(Choices A, C, D and E) MEN1 is characterized by anterior pituitary adenomas, primary hyperparathyroidism (due to parathyroid adenomas or hyperplasia), and neuroendocrine tumors of the pancreas and gastrointestinal tract (eg, gastrinoma, insulinoma). A number of other tumors are also more frequent in MEN1, including adrenocortical adenomas and neuroendocrine thymomas (thymic carcinoid). However, MEN1 is due to mutations in the *MEN1* gene (not *RET*) and is not associated with MTC.

Educational objective:
Multiple endocrine neoplasia type 2 is caused by germline activating mutations in the *RET* proto-oncogene and frequently results in both medullary thyroid cancer and pheochromocytoma. In patients with undiagnosed pheochromocytoma, induction of anesthesia (eg, preparation for thyroidectomy) can precipitate a catecholamine surge, leading to hypertensive crisis, flash pulmonary edema, and atrial fibrillation.

https://t.me/USMLEWorldStep1

A 3-day-old boy is brought to the emergency department due to vomiting, poor feeding, and progressively worsening lethargy. The parents report that his diapers have a sweet smell unlike what they experienced with their older children. The mother and infant were discharged from the hospital yesterday after a normal pregnancy and spontaneous vaginal delivery. The mother is exclusively breastfeeding. Her other 2 children are healthy and have no medical conditions. On physical examination, the infant is lethargic with dry mucous membranes and generalized hypertonia. Which of the following should be restricted from this infant's diet?

- A. Galactose
- B. Leucine
- C. Methionine
- D. Phenylalanine
- E. Tyrosine

Submit

https://t.me/USMLEWorldStep1

A 3-day-old boy is brought to the emergency department due to vomiting, poor feeding, and progressively worsening lethargy. The parents report that his diapers have a sweet smell unlike what they experienced with their older children. The mother and infant were discharged from the hospital yesterday after a normal pregnancy and spontaneous vaginal delivery. The mother is exclusively breastfeeding. Her other 2 children are healthy and have no medical conditions. On physical examination, the infant is lethargic with dry mucous membranes and generalized hypertonia. Which of the following should be restricted from this infant's diet?

- A. Galactose (14%)
- ✓ B. Leucine (55%)
- C. Methionine (3%)
- D. Phenylalanine (22%)
- E. Tyrosine (3%)

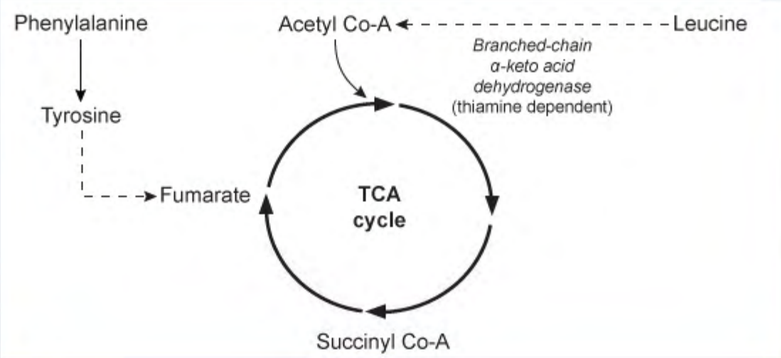
Correct

55% Answered correctly

35 secs Time Spent

2023 Version

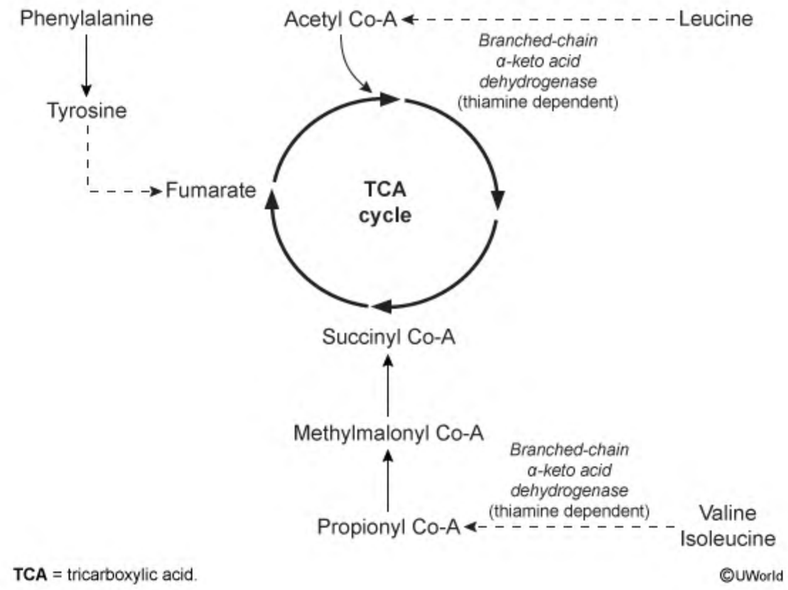
Explanation



https://t.me/USMLEWorldStep1

A 3-day-old boy is brought to the emergency department due to vomiting, poor feeding, and progressively
worse
older
sponta
no me
genera

Exhibit Display



TCA = tricarboxylic acid.

©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Succinyl Co-A

https://t.me/USMLEWorldStep1

TCA = tricarboxylic acid.

©UWorld

This infant has symptoms typical of **maple syrup urine disease**, an autosomal recessive inborn error of metabolism due to branched-chain alpha-keto acid dehydrogenase complex (BCKDC) deficiency. BCKDC is a thiamine-dependent enzyme that helps breakdown the branched-chain amino acids **leucine, isoleucine, and valine** into substrates that can be used in the tricarboxylic acid cycle.

BCKDC deficiency is **neurotoxic** primarily due to elevated levels of leucine. Affected infants present in the first few days of life with progressively worsening irritability, poor feeding, lethargy, and dystonia. The urine is characteristically described as having a maple syrup ("burnt-sugar") odor.

Diagnosis can be confirmed by the presence of **elevated branched-chain amino acid (BCAA) levels**. Therapy consists of **dietary restriction** of BCAAs. Patients remain at lifelong risk for neurotoxicity in the setting of intercurrent illnesses and fasting because these conditions increase the relative rate of protein breakdown, resulting in an increased plasma concentration of BCAAs.

(Choice A) Galactosemia is an autosomal recessive disorder due to galactose-1-phosphate uridyltransferase deficiency. The buildup of galactose (normally found in breast milk and regular infant formula) leads to neonatal jaundice, cataracts, hepatomegaly, and frequently *Escherichia coli* sepsis. Dietary restriction of galactose is the mainstay of treatment.

(Choice C) Homocystinuria is an autosomal recessive disorder marked by a defect in cystathionine beta-synthase, resulting in elevated levels of homocysteine and methionine. Patients have marfanoid appearance (eg, long limbs, arachnodactyly), developmental delay, lens dislocation, and increased risk for thromboembolism. Restriction of methionine for these patients is one aspect of therapy.

(Choice D) Phenylketonuria is an autosomal recessive disorder characterized by phenylalanine hydroxylase deficiency, leading to hyperphenylalaninemia. Untreated patients develop intellectual disability, seizures, decreased hair and skin pigmentation, and a musty odor.

(Choice E) Dietary tyrosine restriction may be beneficial for patients with hypertyrosinemia (progressive liver and renal disease) or alkaptonuria (pigmented osteoarthritis).

Educational objective:

https://t.me/USMLEWorldStep1

thiamine-dependent enzyme that helps breakdown the branched-chain amino acids **leucine, isoleucine, and valine** into substrates that can be used in the tricarboxylic acid cycle.

BCKDC deficiency is **neurotoxic** primarily due to elevated levels of leucine. Affected infants present in the first few days of life with progressively worsening irritability, poor feeding, lethargy, and dystonia. The urine is characteristically described as having a maple syrup ("burnt-sugar") odor.

Diagnosis can be confirmed by the presence of **elevated branched-chain amino acid (BCAA) levels**. Therapy consists of **dietary restriction** of BCAAs. Patients remain at lifelong risk for neurotoxicity in the setting of intercurrent illnesses and fasting because these conditions increase the relative rate of protein breakdown, resulting in an increased plasma concentration of BCAAs.

(Choice A) Galactosemia is an autosomal recessive disorder due to galactose-1-phosphate uridyltransferase deficiency. The buildup of galactose (normally found in breast milk and regular infant formula) leads to neonatal jaundice, cataracts, hepatomegaly, and frequently *Escherichia coli* sepsis. Dietary restriction of galactose is the mainstay of treatment.

(Choice C) Homocystinuria is an autosomal recessive disorder marked by a defect in cystathionine beta-synthase, resulting in elevated levels of homocysteine and methionine. Patients have marfanoid appearance (eg, long limbs, arachnodactyly), developmental delay, lens dislocation, and increased risk for thromboembolism. Restriction of methionine for these patients is one aspect of therapy.

(Choice D) Phenylketonuria is an autosomal recessive disorder characterized by phenylalanine hydroxylase deficiency, leading to hyperphenylalaninemia. Untreated patients develop intellectual disability, seizures, decreased hair and skin pigmentation, and a musty odor.

(Choice E) Dietary tyrosine restriction may be beneficial for patients with hypertyrosinemia (progressive liver and renal disease) or alkaptonuria (pigmented osteoarthritis).

Educational objective:
Maple syrup urine disease classically presents within the first few days of life with irritability, dystonia, poor feeding, and sweet-smelling urine. Dietary restriction of branched-chain amino acids (eg, leucine, isoleucine, valine) is the mainstay of treatment.

https://t.me/USMLEWorldStep1

A 61-year-old woman comes to the office due to a neck lump. She is otherwise in good health and has no other symptoms. Temperature is 36.7 C (98.1 F), blood pressure is 115/70 mm Hg, and pulse is 78/min. On physical examination, there is a nontender, firm nodule in the left lobe of the thyroid. Laboratory results show a normal serum TSH level. Thyroid ultrasonography reveals a 2-cm, hypoechoic thyroid nodule with increased central blood flow. Fine-needle aspiration biopsy shows clusters of cells with large, overlapping nuclei containing finely dispersed chromatin. Numerous intranuclear inclusion bodies and grooves are also seen. Which of the following is the most likely diagnosis?

- A. Anaplastic carcinoma
- B. Colloid nodule
- C. Follicular adenoma
- D. Follicular carcinoma
- E. Medullary carcinoma
- F. Papillary carcinoma

Submit

https://t.me/USMLEWorldStep1

A 61-year-old woman comes to the office due to a neck lump. She is otherwise in good health and has no other symptoms. Temperature is 36.7 C (98.1 F), blood pressure is 115/70 mm Hg, and pulse is 78/min. On physical examination, there is a nontender, firm nodule in the left lobe of the thyroid. Laboratory results show a normal serum TSH level. Thyroid ultrasonography reveals a 2-cm, hypoechoic thyroid nodule with increased central blood flow. Fine-needle aspiration biopsy shows clusters of cells with large, overlapping nuclei containing finely dispersed chromatin. Numerous intranuclear inclusion bodies and grooves are also seen. Which of the following is the most likely diagnosis?

- A. Anaplastic carcinoma (8%)
- ✕ B. Colloid nodule (3%)
- C. Follicular adenoma (11%)
- D. Follicular carcinoma (10%)
- E. Medullary carcinoma (10%)
- ✓ F. Papillary carcinoma (55%)

Incorrect
Correct answer
F

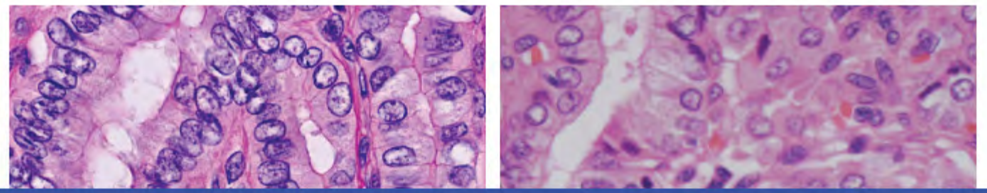
55%
Answered correctly

02 secs
Time Spent

2023
Version

Explanation

Papillary thyroid carcinoma



https://t.me/USMLEWorldStep1

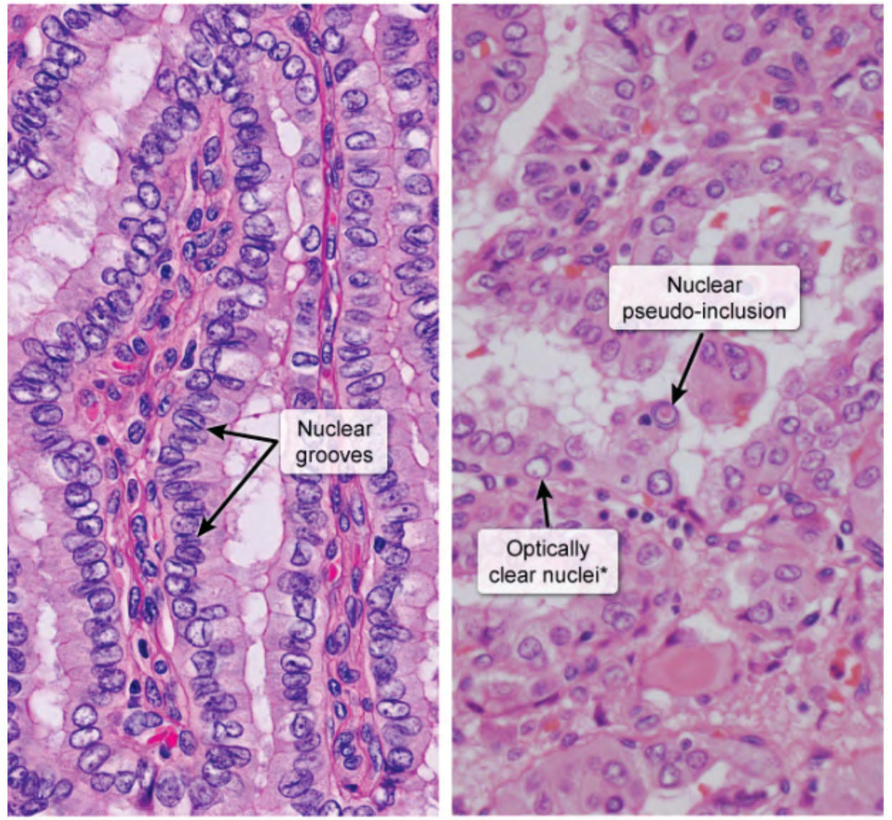
A 61-year-old woman comes to the office due to a neck lump. She is otherwise in good health and has no other sympt
exami
serum
flow. F
disper
is the

Incc
Corre
F

Expl

Exhibit Display

Papillary thyroid carcinoma



*Referred to as ground-glass or Orphan Annie eye nuclei.

©UWorld

Zoom In Zoom Out Reset New | Existing My Notebook

https://t.me/USMLEWorldStep1

The 4 main types of primary **thyroid carcinoma** include papillary, follicular, medullary (derived from the parafollicular, calcitonin-secreting C cells), and anaplastic. The **papillary type** is most common, accounting for >70% of cases. Risk factors include a positive family history of thyroid cancer and radiation exposure, especially in childhood.

Papillary carcinoma cells are characteristically large with overlapping nuclei containing **finely dispersed chromatin**, giving them an empty or ground-glass appearance (sometimes termed **Orphan Annie eye** nuclei after a cartoon character whose eyes were drawn without pupils or irises). Numerous **nuclear grooves** as well as **intranuclear inclusions** composed of cytoplasm (ie, pseudoinclusions) can be seen due to invagination of the nuclear membrane. Psammoma bodies (laminated calcium deposits) may also be found within the tumor.

(Choice A) Anaplastic thyroid carcinoma is an aggressive tumor with a very poor prognosis. It is most common in patients age >60. Cytologic features include markedly pleomorphic cells, including irregular giant and spindle cells.

(Choice B) Most benign thyroid nodules are colloid nodules formed from focal hyperplasia of normal thyroid follicular cells. On cytopathology, a colloid nodule consists of variable-sized thyroid follicles, colloid, and macrophages.

(Choices C and D) Follicular neoplasms lack the characteristic nuclear features and psammoma bodies found in papillary carcinoma. Distinguishing a benign follicular adenoma from a well-differentiated follicular carcinoma depends on the presence of vascular or capsular invasion, which cannot be determined on a fine-needle aspiration specimen.

(Choice E) Medullary thyroid carcinoma appears histologically as polygonal or spindle-shaped cells with a slightly granular cytoplasm that stains for calcitonin. Extracellular amyloid deposits consisting of calcitonin polypeptide may also be seen. Medullary thyroid cancer is a component of multiple endocrine neoplasia types 2A and 2B.

Educational objective:
Papillary thyroid carcinoma is the most common type of thyroid cancer. Characteristic microscopic features include large cells with nuclei containing finely dispersed chromatin, giving them an empty or ground-glass appearance (ie, Orphan Annie eye), as well as intranuclear inclusions and nuclear grooves.

Pathology Endocrine, Diabetes & Metabolism Thyroid cancer

https://t.me/USMLEWorldStep1

The 4 main types of primary **thyroid carcinoma** include papillary, follicular, medullary (derived from the parafollicular, calcitonin-secreting C cells), and anaplastic. The **papillary type** is most common, accounting for >70% childh

Papilla **chrom** a carc **intran** nuclea

(Choi patien

(Choi follicul macro

(Choi papilla depen specin

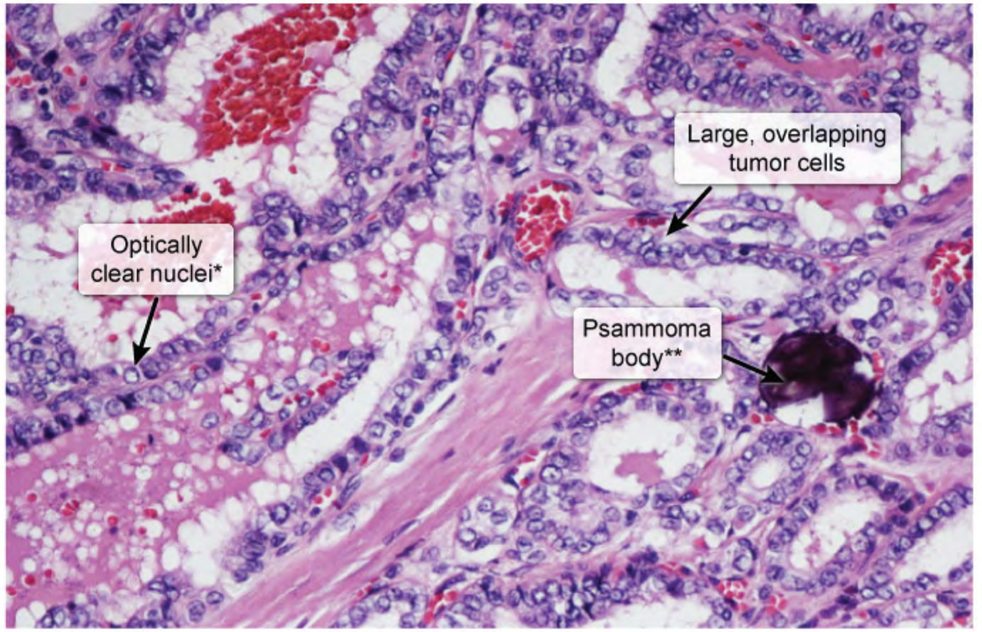
(Choi granul may a

Educa Papilla large Orpha

Pathology Endocrine, Diabetes & Metabolism Thyroid cancer

Exhibit Display

Papillary thyroid carcinoma



*Referred to as ground-glass or Orphan Annie eye nuclei
**Laminated calcification

©UWorld

Zoom In Zoom Out Reset New | Existing My Notebook

https://t.me/USMLEWorldStep1

The 4 main types of primary **thyroid carcinoma** include papillary, follicular, medullary (derived from the parafollicular, calcitonin-secreting C cells), and anaplastic. The **papillary type** is most common, accounting for >70% childh

Papilla **chrom** a carc **intran** nuclea

(Choi patien

(Choi follicul macro

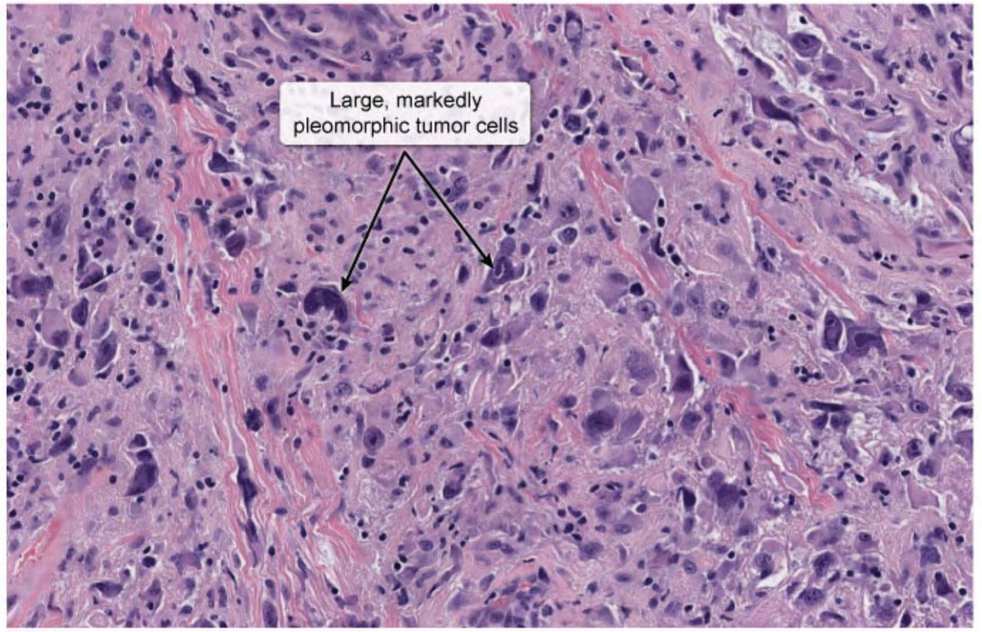
(Choi papilla depen specin

(Choi granul may a

Educa Papilla large Orpha

Exhibit Display

Anaplastic thyroid carcinoma



©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Pathology | Endocrine, Diabetes & Metabolism | Thyroid cancer

https://t.me/USMLEWorldStep1

The 4 main types of primary **thyroid carcinoma** include papillary, follicular, medullary (derived from the parafollicular, calcitonin-secreting C cells), and anaplastic. The **papillary type** is most common, accounting for >70% childh

Papilla **chrom** a carc **intran** nuclea

(Choi patien

(Choi follicul macro

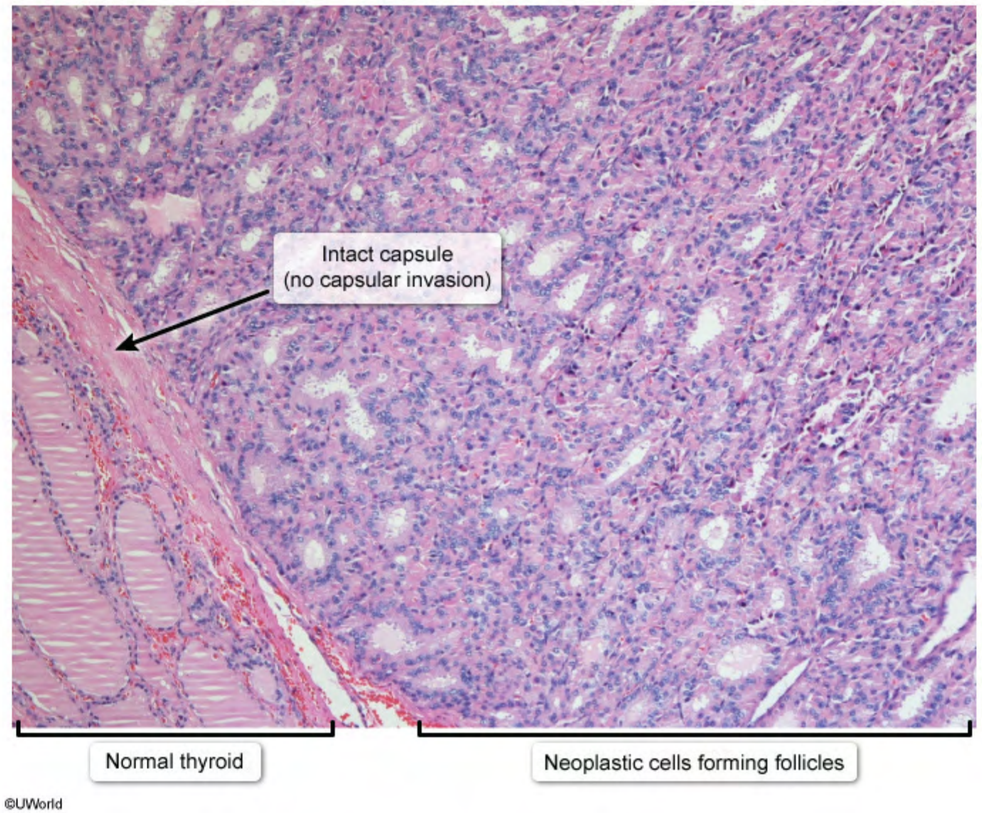
(Choi papilla depen specin

(Choi granul may a

Educa Papilla large Orpha

Exhibit Display

Follicular adenoma



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Pathology | Endocrine, Diabetes & Metabolism | Thyroid cancer

https://t.me/USMLEWorldStep1

The 4 main types of primary **thyroid carcinoma** include papillary, follicular, medullary (derived from the parafollicular, calcitonin-secreting C cells), and anaplastic. The **papillary type** is most common, accounting for >70% childh

Papilla **chrom** a carc **intran** nuclea

(Choi patien

(Choi follicul macro

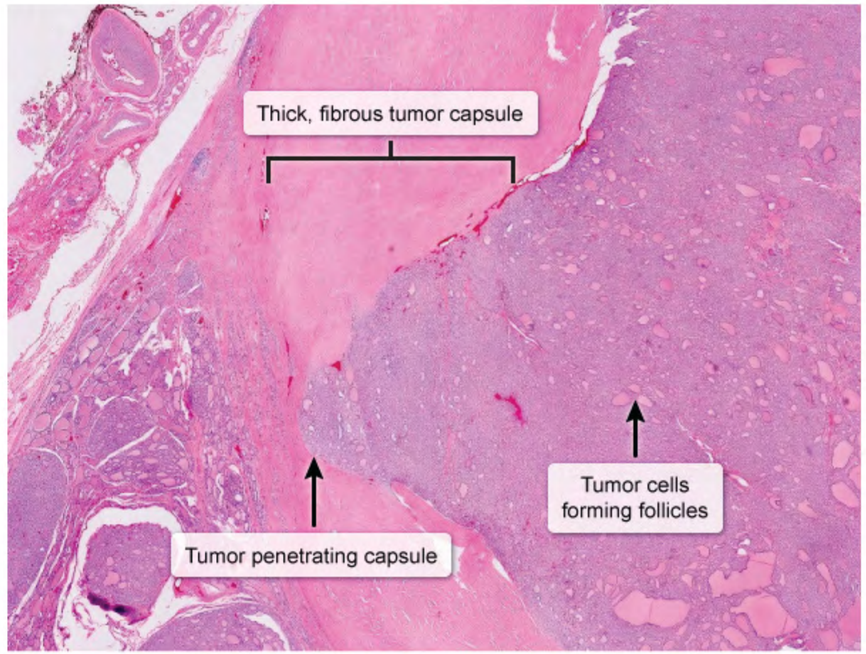
(Choi papilla depen specin

(Choi granul may a

Educa Papilla large Orpha

Exhibit Display

Follicular thyroid carcinoma



©UWorld

Zoom In Zoom Out Reset New | Existing My Notebook

Pathology Endocrine, Diabetes & Metabolism Thyroid cancer

https://t.me/USMLEWorldStep1

The 4 main types of primary **thyroid carcinoma** include papillary, follicular, medullary (derived from the parafollicular, calcitonin-secreting C cells), and anaplastic. The **papillary type** is most common, accounting for >70% childh

Papilla **chrom** a carc **intran** nuclea

(Choi patien

(Choi follicul macro

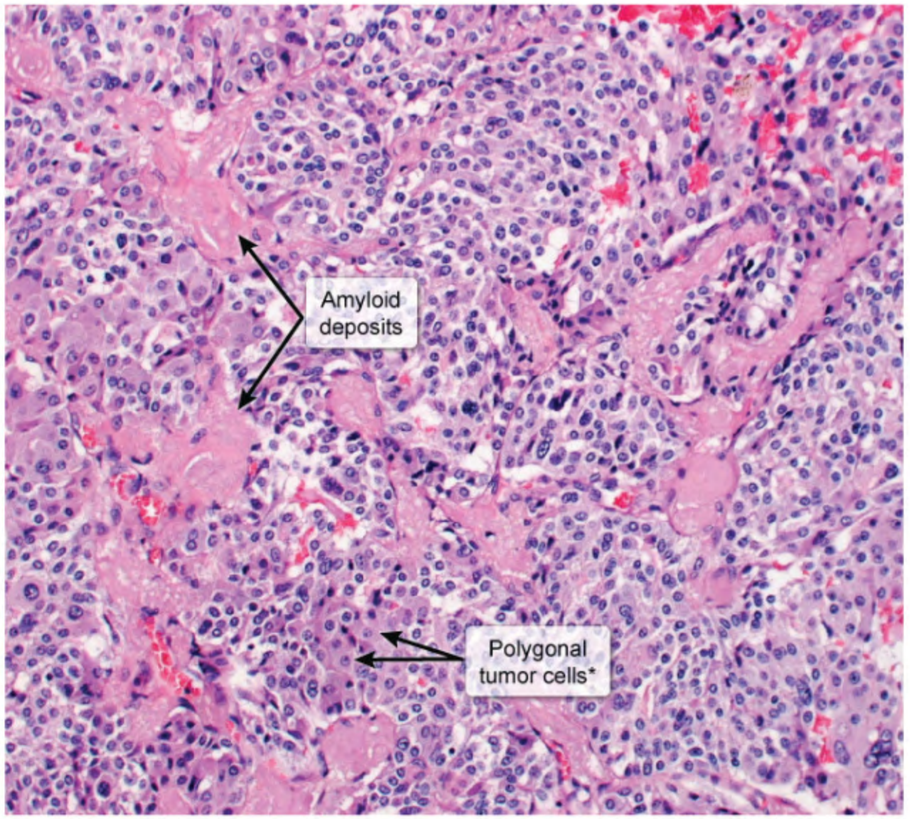
(Choi papilla depen specin

(Choi granul may a

Educa Papilla large Orpha

Exhibit Display

Medullary thyroid carcinoma



*Derived from C (parafollicular) cells

©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Pathology | Endocrine, Diabetes & Metabolism | Thyroid cancer

https://t.me/USMLEWorldStep1

A 30-year-old woman comes to the office due to excessive weight gain without any changes in her diet or physical activity. She has also been feeling more tired lately and has had frequent constipation. The patient has no prior medical problems and takes no medications. She has been pregnant once and gave birth to a healthy infant 3 years ago. Family history is significant for a thyroid disorder in her mother. Blood pressure is 116/90 mm Hg and pulse is 58/min. BMI is 28.5 kg/m^2. Physical examination reveals a diffusely enlarged and nontender thyroid with no nodules. There is delayed relaxation of deep tendon reflexes. Her hair is thin and the skin appears dry. Which of the following sets of laboratory findings is most likely to be seen in this patient?

	TSH	Thyroxine (T4)	Triiodothyronine (T3)
○ A.	Increased	Decreased	Normal
○ B.	Increased	Normal	Normal
○ C.	Increased	Increased	Increased
○ D.	Normal	Normal	Decreased
○ E.	Decreased	Increased	Increased
○ F.	Decreased	Normal	Normal

Submit

https://t.me/USMLEWorldStep1

A 30-year-old woman comes to the office due to excessive weight gain without any changes in her diet or physical activity. She has also been feeling more tired lately and has had frequent constipation. The patient has no prior medical problems and takes no medications. She has been pregnant once and gave birth to a healthy infant 3 years ago. Family history is significant for a thyroid disorder in her mother. Blood pressure is 116/90 mm Hg and pulse is 58/min. BMI is 28.5 kg/m^2. Physical examination reveals a diffusely enlarged and nontender thyroid with no nodules. There is delayed relaxation of deep tendon reflexes. Her hair is thin and the skin appears dry. Which of the following sets of laboratory findings is most likely to be seen in this patient?

		TSH	Thyroxine (T4)	Triiodothyronine (T3)	
✓	A.	Increased	Decreased	Normal	(83%)
	B.	Increased	Normal	Normal	(2%)
	C.	Increased	Increased	Increased	(1%)
	D.	Normal	Normal	Decreased	(8%)
	E.	Decreased	Increased	Increased	(2%)
	F.	Decreased	Normal	Normal	(0%)

Correct

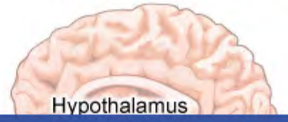
83% Answered correctly

03 secs Time Spent

2023 Version

Explanation

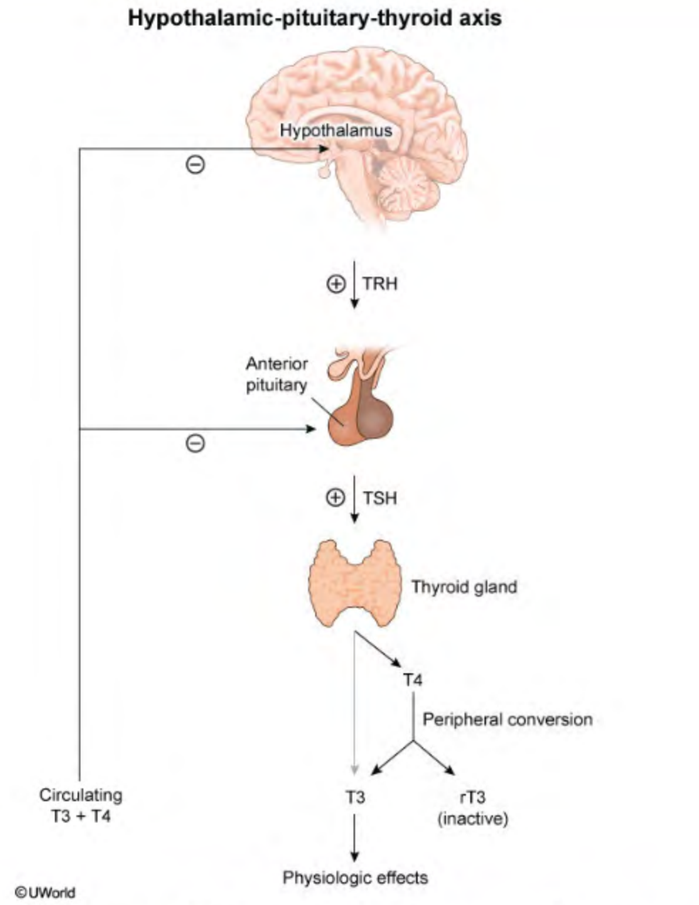
Hypothalamic-pituitary-thyroid axis



https://t.me/USMLEWorldStep1

of the following sets of laboratory findings is most likely to be seen in this patient?

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Cor

Expl

Anterior

https://t.me/USMLEWorldStep1

©UWorld

Regulation of thyroid hormone secretion involves feedback inhibition along the hypothalamic-pituitary-thyroid axis. The hypothalamus releases thyrotropin-releasing hormone (TRH), which triggers release of TSH from the pituitary. TSH stimulates secretion of thyroid hormone from the thyroid, which in turn inhibits release of both TRH and TSH. Thyroid hormone exists in 2 primary forms: T4 (thyroxine), the predominant form secreted by the thyroid, and T3 (triiodothyronine), the more active form produced mainly by deiodination of T4 in peripheral tissues.

This patient has a very typical presentation of **primary hypothyroidism** with weight gain, fatigue, and a delayed relaxation phase of deep tendon reflexes. Her diffuse goiter suggests chronic autoimmune (Hashimoto) thyroiditis, which is the most common cause of hypothyroidism in developed countries. As autoimmune destruction of the gland progresses, thyroid hormone production declines, leading to loss of feedback inhibition of TSH secretion; therefore, patients have **low T4** and **elevated TSH** levels. However, because T3 is produced mainly in peripheral tissues and has a short half-life, serum T3 levels fluctuate widely and correlate poorly with clinical status; **T3 is often normal** in primary hypothyroidism.

(Choice B) TSH secretion is very sensitive to changes in thyroid status and rises in response to even small declines in thyroid hormone production. Subclinical hypothyroidism is a common biochemical state in which an elevated TSH is necessary to maintain normal thyroid hormone levels. However, most patients are asymptomatic.

(Choices C, E, and F) Primary hyperthyroidism (eg, Graves disease) is characterized by elevated thyroid hormone levels and suppressed TSH. Subclinical hyperthyroidism is characterized by suppressed TSH with normal thyroid hormone levels. Central (secondary) hyperthyroidism (eg, TSH-secreting pituitary adenoma) shows elevated levels of both TSH and thyroid hormone. Common clinical features of hyperthyroidism (primary or secondary) include weight loss, heat intolerance, and tachycardia; patients with subclinical hyperthyroidism may be asymptomatic or have mild symptoms. T3 levels correlate with clinical status in hyperthyroidism more closely than in hypothyroidism and are often elevated.

(Choice D) Euthyroid sick syndrome is a constellation of abnormal thyroid tests seen in patients with severe systemic illness (eg, sepsis). Excess cortisol, inflammatory cytokines, starvation, and certain medications (eg, amiodarone) can cause reduced conversion of T4 to T3, leading to low serum T3; reverse T3 (the inactive metabolite of T4) is typically elevated but TSH and T4 are usually normal.

Educational objective:

https://t.me/USMLEWorldStep1

relaxation phase of deep tendon reflexes. Her diffuse goiter suggests chronic autoimmune (Hashimoto) thyroiditis, which is the most common cause of hypothyroidism in developed countries. As autoimmune destruction of the gland progresses, thyroid hormone production declines, leading to loss of feedback inhibition of TSH secretion; therefore, patients have **low T4** and **elevated TSH** levels. However, because T3 is produced mainly in peripheral tissues and has a short half-life, serum T3 levels fluctuate widely and correlate poorly with clinical status; **T3 is often normal** in primary hypothyroidism.

(Choice B) TSH secretion is very sensitive to changes in thyroid status and rises in response to even small declines in thyroid hormone production. Subclinical hypothyroidism is a common biochemical state in which an elevated TSH is necessary to maintain normal thyroid hormone levels. However, most patients are asymptomatic.

(Choices C, E, and F) Primary hyperthyroidism (eg, Graves disease) is characterized by elevated thyroid hormone levels and suppressed TSH. Subclinical hyperthyroidism is characterized by suppressed TSH with normal thyroid hormone levels. Central (secondary) hyperthyroidism (eg, TSH-secreting pituitary adenoma) shows elevated levels of both TSH and thyroid hormone. Common clinical features of hyperthyroidism (primary or secondary) include weight loss, heat intolerance, and tachycardia; patients with subclinical hyperthyroidism may be asymptomatic or have mild symptoms. T3 levels correlate with clinical status in hyperthyroidism more closely than in hypothyroidism and are often elevated.

(Choice D) Euthyroid sick syndrome is a constellation of abnormal thyroid tests seen in patients with severe systemic illness (eg, sepsis). Excess cortisol, inflammatory cytokines, starvation, and certain medications (eg, amiodarone) can cause reduced conversion of T4 to T3, leading to low serum T3; reverse T3 (the inactive metabolite of T4) is typically elevated but TSH and T4 are usually normal.

Educational objective:
Primary hypothyroidism is characterized by decreased T4 levels and increased TSH. T3 is primarily produced by conversion from T4 in peripheral tissues; serum levels widely fluctuate due to its short half life, and can often be within the normal range in patients with hypothyroidism.

References

- Pitfalls in the measurement and interpretation of thyroid function tests

https://t.me/USMLEWorldStep1

A 34-year-old, previously healthy woman comes to the office due to irregular menstruation and a 4.5 kg (10-lb) weight gain over the past 6 months. The patient also reports muscle weakness causing difficulty climbing stairs or lifting her child. Blood pressure is 152/86 mm Hg and pulse is 72/min. BMI is 31 kg/m^2. Physical examination shows excessive fat accumulation in the abdomen and supraclavicular area. Sun-exposed areas and skin creases are hyperpigmented and there are wide striae over the abdomen. Coarse hair is present on the face, chest, and abdomen. Which of the following sets of laboratory findings are most likely to be seen in this patient?

	24-hour urinary cortisol	Serum ACTH	Serum DHEAS
A.	↑	↑	↑
B.	↓	↑	↓
C.	↑	↓	↓
D.	Normal	Normal	↑
E.	↓	↓	↓

Submit

https://t.me/USMLEWorldStep1

A 34-year-old, previously healthy woman comes to the office due to irregular menstruation and a 4.5 kg (10-lb) weight gain over the past 6 months. The patient also reports muscle weakness causing difficulty climbing stairs or lifting her child. Blood pressure is 152/86 mm Hg and pulse is 72/min. BMI is 31 kg/m². Physical examination shows excessive fat accumulation in the abdomen and supraclavicular area. Sun-exposed areas and skin creases are hyperpigmented and there are wide striae over the abdomen. Coarse hair is present on the face, chest, and abdomen. Which of the following sets of laboratory findings are most likely to be seen in this patient?

	24-hour urinary cortisol	Serum ACTH	Serum DHEAS	
✓ A.	↑	↑	↑	(79%)
B.	↓	↑	↓	(3%)
C.	↑	↓	↓	(14%)
D.	Normal	Normal	↑	(1%)
E.	↓	↓	↓	(0%)

Correct

79% Answered correctly

03 secs Time Spent

2023 Version

Explanation

Categorization of Cushing syndrome		
	Etiology	**Distinguishing findings**
ACTH dependent	• Cushing disease (ACTH-secreting pituitary adenoma)	• Hyperpigmentation • Hyperandrogenism (eg, hirsutism, oligomenorrhea/amenorrhea)

https://t.me/USMLEWorldStep1

Categorization of Cushing syndrome		
	Etiology	**Distinguishing findings**
ACTH dependent	• Cushing disease (ACTH-secreting pituitary adenoma) • Ectopic ACTH secretion	• Hyperpigmentation • Hyperandrogenism (eg, hirsutism, oligomenorrhea/amenorrhea) • ↑ ACTH
ACTH independent	• Adrenal mass (adenoma or carcinoma) • Exogenous glucocorticoids	• ↓ ACTH

This patient with central obesity, proximal muscle weakness, striae, and hypertension has common features of cortisol excess (ie, Cushing syndrome). Other possible findings include hyperglycemia, dermal atrophy, and easy bruisability. Hypercortisolism can be confirmed on finding an elevated late-night salivary cortisol concentration or **increased 24-hour urine cortisol** excretion.

Cushing syndrome can be categorized as ACTH-dependent (ie, ↑**ACTH** stimulating excess cortisol production) or ACTH-independent (ie, glucocorticoid excess not caused by ACTH). Excess ACTH secretion causes identifiable clinical findings:

- **Hyperpigmentation:** Both ACTH and alpha-melanocyte-stimulating hormone (MSH) are derived from pro-opiomelanocortin, leading to cosecretion of alpha-MSH. ACTH also directly stimulates the MC2R receptor on melanocytes.
- Androgenization: ACTH stimulates production of adrenal androgens (eg, ↑**DHEAS** [dehydroepiandrosterone sulfate], androstenedione). This leads to **hirsutism**, **menstrual abnormalities**, and oily skin.

This patient's hyperpigmentation and hirsutism are consistent with ACTH-dependent hypercortisolism, likely due to a corticotroph pituitary adenoma (**Cushing disease**).

(Choice B) Primary adrenal insufficiency leads to decreased cortisol levels (and decreased urinary cortisol excretion) with a compensatory rise in ACTH. Hyperpigmentation may be present, but adrenal androgen production is often diminished (due to loss of androgen-producing adrenocortical cells) and hirsutism is not

https://t.me/USMLEWorldStep1

- **Hyperpigmentation:** Both ACTH and alpha-melanocyte-stimulating hormone (MSH) are derived from pro-opiomelanocortin, leading to cosecretion of alpha-MSH. ACTH also directly stimulates the MC2R receptor on melanocytes.
- Androgenization: ACTH stimulates production of adrenal androgens (eg, ↑**DHEAS** [dehydroepiandrosterone sulfate], androstenedione). This leads to **hirsutism**, **menstrual abnormalities**, and oily skin.

This patient's hyperpigmentation and hirsutism are consistent with ACTH-dependent hypercortisolism, likely due to a corticotroph pituitary adenoma (**Cushing disease**).

(Choice B) Primary adrenal insufficiency leads to decreased cortisol levels (and decreased urinary cortisol excretion) with a compensatory rise in ACTH. Hyperpigmentation may be present, but adrenal androgen production is often diminished (due to loss of androgen-producing adrenocortical cells) and hirsutism is not present.

(Choices C and E) ACTH-independent Cushing syndrome due to a cortisol-producing adrenal adenoma is characterized by increased urinary cortisol excretion with suppressed ACTH levels. Exogenous glucocorticoids also cause suppression of ACTH, but with decreased production (and urinary excretion) of cortisol. Low cortisol excretion and ACTH levels are also seen in central adrenal insufficiency. Because ACTH is low in these states, patients do not have hyperpigmentation or hyperandrogenic features (eg, hirsutism).

(Choice D) Polycystic ovary syndrome is characterized by excessive ovarian production of androgens. Common clinical features include oligo/amenorrhea, obesity, and hirsutism. However, ACTH and cortisol production are unaffected, and hyperpigmentation is not seen.

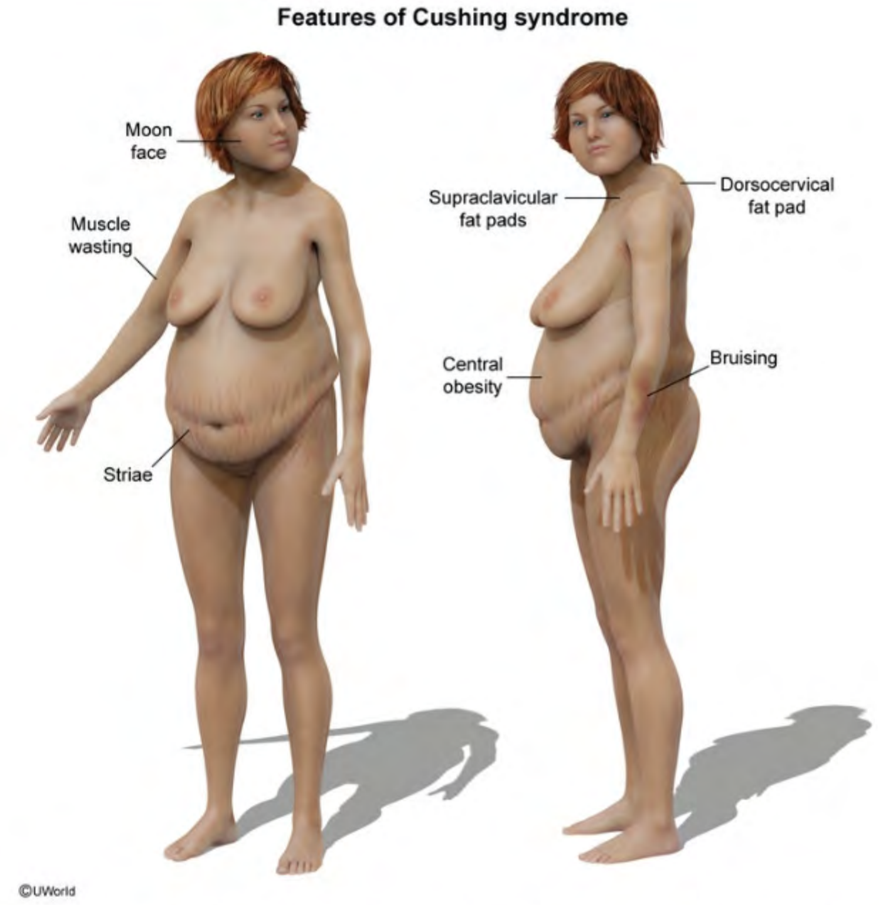
Educational objective:
Cushing syndrome can be categorized as ACTH-dependent or ACTH-independent. Excess ACTH secretion in ACTH-dependent Cushing syndrome leads to hyperpigmentation. In addition to increased cortisol production, ACTH stimulates production of adrenal androgens (eg, testosterone, dehydroepiandrosterone sulfate) leading to hirsutism and menstrual irregularities.

References

https://t.me/USMLEWorldStep1

Explanation

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

This p
cortisc
bruisa
increa

Cushir
ACTH
clinica

- **H**
  o
  m
- A
  su

This patient's hyperpigmentation and hirsutism are consistent with ACTH-dependent hypercortisolism, likely due to a corticotroph pituitary adenoma (**Cushing disease**).

https://t.me/USMLEWorldStep1

A 48-year-old woman comes to the office for follow-up of primary hypothyroidism due to chronic autoimmune (Hashimoto) thyroiditis. She feels well and has no palpitations, heat/cold intolerance, diarrhea/constipation, or changes in weight. The patient takes levothyroxine daily on an empty stomach. She has no other medical conditions and takes no other medications. The patient has no drug allergies and does not use tobacco, alcohol, or illicit drugs. Blood pressure is 120/70 mm Hg and pulse is 72/min. BMI is 27 kg/m^2. On physical examination, the thyroid is normal to palpation. There is no peripheral edema. Laboratory results show a serum TSH level of <0.01 μU/mL. Maintaining the current dose of levothyroxine would put this patient at the greatest risk for which of the following complications?

- A. Agranulocytosis
- B. Atrial fibrillation
- C. Dementia
- D. Goiter
- E. Hepatotoxicity
- F. Thyroid cancer

Submit

https://t.me/USMLEWorldStep1

A 48-year-old woman comes to the office for follow-up of primary hypothyroidism due to chronic autoimmune (Hashimoto) thyroiditis. She feels well and has no palpitations, heat/cold intolerance, diarrhea/constipation, or changes in weight. The patient takes levothyroxine daily on an empty stomach. She has no other medical conditions and takes no other medications. The patient has no drug allergies and does not use tobacco, alcohol, or illicit drugs. Blood pressure is 120/70 mm Hg and pulse is 72/min. BMI is 27 kg/m^2. On physical examination, the thyroid is normal to palpation. There is no peripheral edema. Laboratory results show a serum TSH level of <0.01 μU/mL. Maintaining the current dose of levothyroxine would put this patient at the greatest risk for which of the following complications?

- ✗ A. Agranulocytosis (13%)
- ✓ B. Atrial fibrillation (53%)
- C. Dementia (2%)
- D. Goiter (17%)
- E. Hepatotoxicity (8%)
- F. Thyroid cancer (4%)

Incorrect
Correct answer
B

53%
Answered correctly

04 secs
Time Spent

2023
Version

Explanation

Cardiovascular effects of hyperthyroidism	
Increased rate	• Tachycardia/palpitations • Atrial fibrillation
	• ↑ Ejection fraction & cardiac output

https://t.me/USMLEWorldStep1

Cardiovascular effects of hyperthyroidism	
Increased rate	• Tachycardia/palpitations • Atrial fibrillation
Increased contractility	• ↑ Ejection fraction & cardiac output • ↑ Myocardial oxygen demand & angina • ↑ Pulmonary artery pressure
Peripheral vasodilation	• ↓ Systemic vascular resistance
Additional effects	• ↓ Diastolic pressure • ↑ Systolic pressure • ↑ Pulse pressure • High-output heart failure

This patient is on **thyroid replacement therapy** for hypothyroidism and has a **suppressed TSH** (normal range: 0.5 to 5.0 μU/mL), indicating that her **current dose is too high**. Excess thyroid hormone, whether due to endogenous hyperthyroidism or iatrogenic over-replacement with levothyroxine, causes increased beta-adrenergic receptor expression. The resulting **hyperadrenergic state** can lead to significant cardiovascular complications.

Thyrotoxicosis is associated with hypertension, tachycardia, and increased myocyte automaticity. **Atrial fibrillation** is the most common supraventricular arrhythmia and is a frequent complication of thyrotoxicosis. Thyrotoxicosis also increases contractility, which increases myocardial oxygen demand and can **precipitate angina** in patients with underlying coronary disease. It can also increase cardiac output (while also decreasing systemic vascular resistance) and lead to **high-output heart failure**. Therefore, even though this patient feels well, her dose of levothyroxine should be reduced to avoid long-term complications of over-replacement.

(Choices A and E) Agranulocytosis is a potential complication of thionamide antithyroid drugs (eg, propylthiouracil, methimazole). Propylthiouracil can also cause hepatotoxicity. However, levothyroxine used in thyroid replacement therapy does not cause these complications.

(Choice C) Thyroid over-replacement can cause insomnia and affective symptoms (eg, anxiety, irritability).

https://t.me/USMLEWorldStep1

This patient is on **thyroid replacement therapy** for hypothyroidism and has a **suppressed TSH** (normal range: 0.5 to 5.0 μU/mL), indicating that her **current dose is too high**. Excess thyroid hormone, whether due to endogenous hyperthyroidism or iatrogenic over-replacement with levothyroxine, causes increased beta-adrenergic receptor expression. The resulting **hyperadrenergic state** can lead to significant cardiovascular complications.

Thyrotoxicosis is associated with hypertension, tachycardia, and increased myocyte automaticity. **Atrial fibrillation** is the most common supraventricular arrhythmia and is a frequent complication of thyrotoxicosis. Thyrotoxicosis also increases contractility, which increases myocardial oxygen demand and can **precipitate angina** in patients with underlying coronary disease. It can also increase cardiac output (while also decreasing systemic vascular resistance) and lead to **high-output heart failure**. Therefore, even though this patient feels well, her dose of levothyroxine should be reduced to avoid long-term complications of over-replacement.

(Choices A and E) Agranulocytosis is a potential complication of thionamide antithyroid drugs (eg, propylthiouracil, methimazole). Propylthiouracil can also cause hepatotoxicity. However, levothyroxine used in thyroid replacement therapy does not cause these complications.

(Choice C) Thyroid over-replacement can cause insomnia and affective symptoms (eg, anxiety, irritability). Although hyperthyroidism in elderly patients may manifest as social withdrawal and slowed responses (apathetic depression) resembling dementia, cognitive dysfunction in younger patients is more likely to be seen in hypothyroidism rather than in hyperthyroidism.

(Choice D) The goiter seen in hypothyroidism is due to chronic thyroid stimulation by TSH. This manifestation improves with the administration of levothyroxine (as TSH levels are decreased) and is not seen in over-replacement.

(Choice F) Thyroid cancer is a potential long-term complication of radioiodine therapy for hyperthyroidism.

Educational objective:
Thyrotoxicosis, whether due to endogenous hyperthyroidism or over-replacement with thyroid hormone in patients with hypothyroidism, causes a hyperadrenergic state that can lead to atrial fibrillation, high-output heart failure, and worsening of angina pectoris.

References

https://t.me/USMLEWorldStep1

A 14-year-old boy is brought to the emergency department due to excessive urination and thirst. He has lost 4.5 kg (10 lb) in the last 3 weeks. The patient has no past medical problems. His father has type 1 diabetes mellitus. Physical examination shows dry mucous membranes. Laboratory studies reveal blood glucose of 455 mg/dL, normal anion gap, and hemoglobin A1c of 11.3%. The patient is diagnosed with type 1 diabetes, and treatment with insulin is initiated. In addition to lowering blood glucose, insulin increases glycogen synthesis in hepatocytes. Activation of which of the following molecules most likely promotes this metabolic effect?

- A. Janus kinase (JAK)
- B. Lipoxygenase
- C. Phospholipase C
- D. Protein kinase A
- E. Protein phosphatase

Submit

https://t.me/USMLEWorldStep1

A 14-year-old boy is brought to the emergency department due to excessive urination and thirst. He has lost 4.5 kg (10 lb) in the last 3 weeks. The patient has no past medical problems. His father has type 1 diabetes mellitus. Physical examination shows dry mucous membranes. Laboratory studies reveal blood glucose of 455 mg/dL, normal anion gap, and hemoglobin A1c of 11.3%. The patient is diagnosed with type 1 diabetes, and treatment with insulin is initiated. In addition to lowering blood glucose, insulin increases glycogen synthesis in hepatocytes. Activation of which of the following molecules most likely promotes this metabolic effect?

- ✗ A. Janus kinase (JAK) (23%)
- B. Lipoxygenase (1%)
- C. Phospholipase C (9%)
- D. Protein kinase A (27%)
- ✓ E. Protein phosphatase (38%)

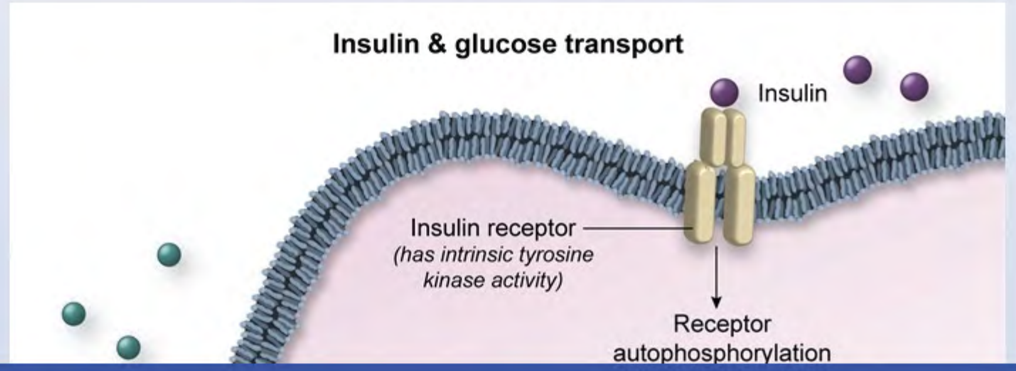
Incorrect
Correct answer
E

38%
Answered correctly

03 secs
Time Spent

2023
Version

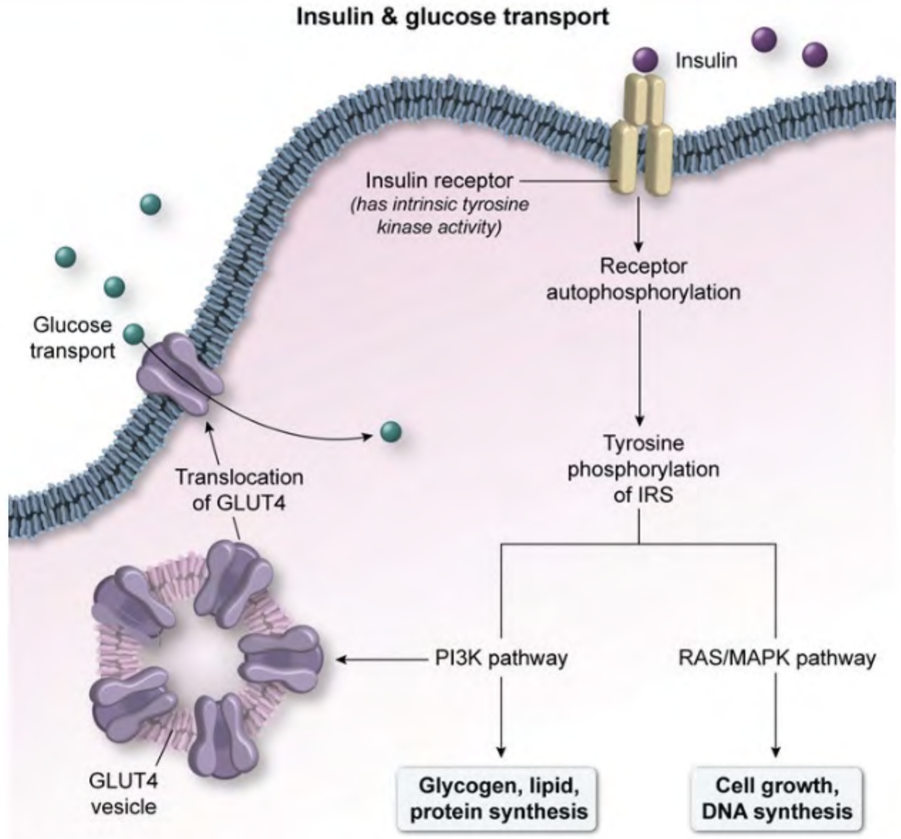
Explanation



https://t.me/USMLEWorldStep1

A 14-year-old boy is brought to the emergency department due to excessive urination and thirst. He has lost 4.5 kg (10
Physic
norma
with in
Activa

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Receptor autophosphorylation

https://t.me/USMLEWorldStep1

Insulin decreases blood glucose levels by increasing glucose uptake into skeletal muscle and adipocytes. In addition to having glucose lowering effects, insulin is an anabolic hormone that promotes synthesis of glycogen, triglycerides, nucleic acids, and proteins. Furthermore, insulin inhibits glycogenolysis and gluconeogenesis.

The surface receptor for insulin is a transmembrane protein with **intrinsic tyrosine kinase** activity in its cytoplasmic domain. Insulin binding activates tyrosine kinase, leading to phosphorylation of insulin receptor substrate 1 (IRS-1). IRS-1 then activates several intracellular pathways that induce the physiologic effects of insulin. Activation of the MAP kinase pathway promotes mitogenic functions such as DNA synthesis and cell growth. In contrast, activation of **phosphatidylinositol-3-kinase (PI3K)** stimulates metabolic functions such as translocation of GLUT-4 to the cell membrane, **glycogen synthesis**, and fat synthesis. PI3K promotes glycogen synthesis by activating **protein phosphatase**, an enzyme that dephosphorylates glycogen synthase, leading to its activation.

(Choice A) Janus kinase (JAK) is a component of the second messenger system for various peptide hormones (eg, growth hormone, prolactin) and cytokines (eg, interferon, interleukin). JAK has tyrosine kinase activity; however, it is a cytoplasmic enzyme that is not part of a cell surface receptor (non-receptor tyrosine kinase).

(Choice B) Lipoxygenase is an enzyme involved in arachidonic acid metabolism and is responsible for the arm of that pathway that synthesizes leukotrienes.

(Choice C) Phospholipase C is activated in the G-protein/inositol triphosphate (IP_3)/calcium second messenger system. Hormone-receptor binding activates a G-protein that in turn activates phospholipase C to degrade phospholipids into IP_3 and diacylglycerol. Both diacylglycerol and the increased intracellular calcium caused by IP_3 lead to protein kinase C activation.

(Choice D) Protein kinase A is the primary intracellular effector enzyme in the G-protein/adenylate cyclase second messenger system. Glucagon acts through this pathway to stimulate glycogen breakdown. Protein kinase A activates glycogen phosphorylase via activation of glycogen phosphorylase kinase.

Educational objective:
Insulin is an anabolic hormone that acts via receptor tyrosine kinase signaling to increase the synthesis of glycogen, proteins, fatty acids, and nucleic acids. Tyrosine kinase/phosphatidylinositol-3-kinase stimulation promotes glycogen synthesis by activating protein phosphatase, an enzyme that dephosphorylates (activates)

https://t.me/USMLEWorldStep1

The surface receptor for insulin is a transmembrane protein with **intrinsic tyrosine kinase** activity in its cytoplasmic domain. Insulin binding activates tyrosine kinase, leading to phosphorylation of insulin receptor substrate 1 (IRS-1). IRS-1 then activates several intracellular pathways that induce the physiologic effects of insulin. Activation of the MAP kinase pathway promotes mitogenic functions such as DNA synthesis and cell growth. In contrast, activation of **phosphatidylinositol-3-kinase (PI3K)** stimulates metabolic functions such as translocation of GLUT-4 to the cell membrane, **glycogen synthesis**, and fat synthesis. PI3K promotes glycogen synthesis by activating **protein phosphatase**, an enzyme that dephosphorylates glycogen synthase, leading to its activation.

(Choice A) Janus kinase (JAK) is a component of the second messenger system for various peptide hormones (eg, growth hormone, prolactin) and cytokines (eg, interferon, interleukin). JAK has tyrosine kinase activity; however, it is a cytoplasmic enzyme that is not part of a cell surface receptor (non-receptor tyrosine kinase).

(Choice B) Lipoxygenase is an enzyme involved in arachidonic acid metabolism and is responsible for the arm of that pathway that synthesizes leukotrienes.

(Choice C) Phospholipase C is activated in the G-protein/inositol triphosphate (IP_3)/calcium second messenger system. Hormone-receptor binding activates a G-protein that in turn activates phospholipase C to degrade phospholipids into IP_3 and diacylglycerol. Both diacylglycerol and the increased intracellular calcium caused by IP_3 lead to protein kinase C activation.

(Choice D) Protein kinase A is the primary intracellular effector enzyme in the G-protein/adenylate cyclase second messenger system. Glucagon acts through this pathway to stimulate glycogen breakdown. Protein kinase A activates glycogen phosphorylase via activation of glycogen phosphorylase kinase.

Educational objective:
Insulin is an anabolic hormone that acts via receptor tyrosine kinase signaling to increase the synthesis of glycogen, proteins, fatty acids, and nucleic acids. Tyrosine kinase/phosphatidylinositol-3-kinase stimulation promotes glycogen synthesis by activating protein phosphatase, an enzyme that dephosphorylates (activates) glycogen synthase.

References

- Role of phosphatidylinositol 3 kinase activation on insulin action and its alteration in diabetic conditions

https://t.me/USMLEWorldStep1

A 42-year-old woman with Graves disease is hospitalized for elective total thyroidectomy. Her hyperthyroid symptoms have been controlled with methimazole and propranolol, but she still has a goiter. The patient has no other medical problems. She undergoes total thyroidectomy without any immediate operative complications and feels well the next day. Laboratory results are as follows:

Serum chemistry

Sodium	141 mEq/L
Potassium	4.4 mEq/L
Creatinine	0.8 mg/dL
Calcium	7.5 mg/dL

Preoperative electrolyte values were within normal limits. Which of the following medications should be started in this patient?

- A. Alendronate
- B. Calcitriol
- C. Cinacalcet
- D. Prednisone
- E. Radioactive iodine
- F. Sevelamer

Submit

https://t.me/USMLEWorldStep1

A 42-year-old woman with Graves disease is hospitalized for elective total thyroidectomy. Her hyperthyroid symptoms have been controlled with methimazole and propranolol, but she still has a goiter. The patient has no other medical problems. She undergoes total thyroidectomy without any immediate operative complications and feels well the next day. Laboratory results are as follows:

Serum chemistry

Sodium	141 mEq/L
Potassium	4.4 mEq/L
Creatinine	0.8 mg/dL
Calcium	7.5 mg/dL

Preoperative electrolyte values were within normal limits. Which of the following medications should be started in this patient?

- ✗ A. Alendronate (5%)
- ✓ B. Calcitriol (66%)
- C. Cinacalcet (19%)
- D. Prednisone (1%)
- E. Radioactive iodine (2%)
- F. Sevelamer (3%)

Incorrect
Correct answer
B

66%
Answered correctly

04 secs
Time Spent

2023
Version

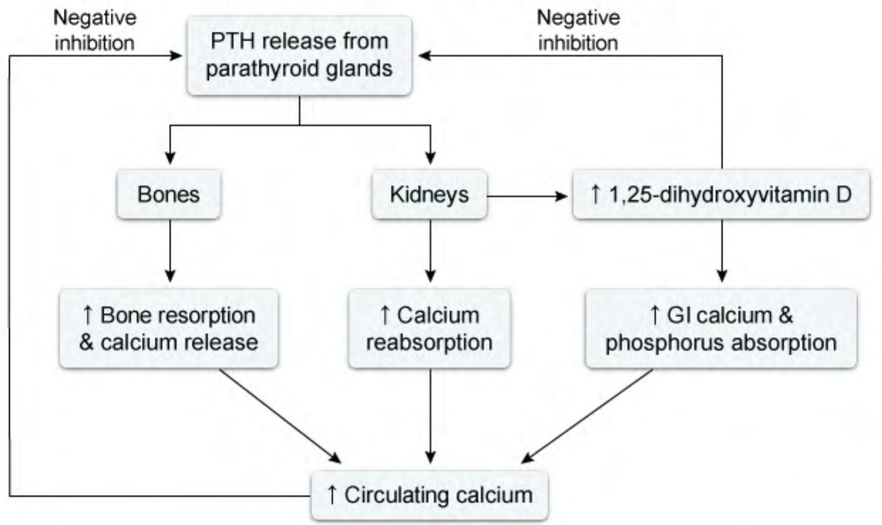
Explanation

https://t.me/USMLEWorldStep1

E. Radioactive iodine (2%)

Exhibit Display

Parathyroid hormone, vitamin D & calcium axis



GI = gastrointestinal; **PTH** = parathyroid hormone.

©UWorld

Zoom In Zoom Out Reset New | Existing My Notebook

Inco
Corre
B

Expl

The pa
direct
hypop
may be asymptomatic initially but can develop paresthesias (of the lips, mouth, hands, and feet), muscle twitching,

https://t.me/USMLEWorldStep1

GI = gastrointestinal; **PTH** = parathyroid hormone.

©UWorld

The **parathyroid glands** are relatively small and indistinct and can be **injured during thyroid surgery** due to direct trauma, devascularization, or inadvertent removal. Transient or permanent postoperative **hypoparathyroidism** can occur following thyroidectomy and cause clinically significant **hypocalcemia**. Patients may be asymptomatic initially but can develop paresthesias (of the lips, mouth, hands, and feet), muscle twitching, or cramps. Worsening hypocalcemia can lead to trismus or tetany with changes in mental status and generalized seizures.

Postoperative supplementation with oral calcium and vitamin D can be used to treat and prevent postoperative hypocalcemia. **Calcitriol**, the active form of vitamin D, should be chosen over calcidiol as the conversion of calcidiol to calcitriol is dependent on parathyroid hormone, and patients with hypoparathyroidism can have inadequate production of calcitriol.

(Choice A) Alendronate is a bisphosphonate that inhibits osteoclast function. Bisphosphonates can worsen hypocalcemia by decreasing the release of calcium from bone.

(Choice C) Cinacalcet is a calcimimetic that allosterically activates the calcium-sensing receptor in the parathyroid gland, decreasing parathyroid hormone release. Cinacalcet is normally used for secondary hyperparathyroidism in patients on dialysis.

(Choice D) Glucocorticoids (eg, prednisone) can worsen hypocalcemia by decreasing expression of the vitamin D receptor.

(Choice E) The primary treatment modalities for Graves disease include antithyroid drugs (eg, methimazole), thyroidectomy, and radioiodine ablation. This patient has undergone definitive treatment with thyroidectomy and has no indication for radioiodine therapy.

(Choice F) Sevelamer is a nonabsorbable phosphate-binding polymer that decreases absorption of phosphate in the gastrointestinal tract, and is used to treat hyperphosphatemia in patients on dialysis. Calcium-based phosphate binders (eg, calcium carbonate, calcium acetate) frequently raise calcium levels, but sevelamer has a lesser effect on calcium and would not be adequate treatment for hypocalcemia.

Educational objective:

Postoperative hypoparathyroidism with resultant hypocalcemia is a common complication of thyroidectomy due to

https://t.me/USMLEWorldStep1

hypoparathyroidism can occur following thyroidectomy and cause clinically significant **hypocalcemia**. Patients may be asymptomatic initially but can develop paresthesias (of the lips, mouth, hands, and feet), muscle twitching, or cramps. Worsening hypocalcemia can lead to trismus or tetany with changes in mental status and generalized seizures.

Postoperative supplementation with oral calcium and vitamin D can be used to treat and prevent postoperative hypocalcemia. **Calcitriol**, the active form of vitamin D, should be chosen over calcidiol as the conversion of calcidiol to calcitriol is dependent on parathyroid hormone, and patients with hypoparathyroidism can have inadequate production of calcitriol.

(Choice A) Alendronate is a bisphosphonate that inhibits osteoclast function. Bisphosphonates can worsen hypocalcemia by decreasing the release of calcium from bone.

(Choice C) Cinacalcet is a calcimimetic that allosterically activates the calcium-sensing receptor in the parathyroid gland, decreasing parathyroid hormone release. Cinacalcet is normally used for secondary hyperparathyroidism in patients on dialysis.

(Choice D) Glucocorticoids (eg, prednisone) can worsen hypocalcemia by decreasing expression of the vitamin D receptor.

(Choice E) The primary treatment modalities for Graves disease include antithyroid drugs (eg, methimazole), thyroidectomy, and radioiodine ablation. This patient has undergone definitive treatment with thyroidectomy and has no indication for radioiodine therapy.

(Choice F) Sevelamer is a nonabsorbable phosphate-binding polymer that decreases absorption of phosphate in the gastrointestinal tract, and is used to treat hyperphosphatemia in patients on dialysis. Calcium-based phosphate binders (eg, calcium carbonate, calcium acetate) frequently raise calcium levels, but sevelamer has a lesser effect on calcium and would not be adequate treatment for hypocalcemia.

Educational objective:
Postoperative hypoparathyroidism with resultant hypocalcemia is a common complication of thyroidectomy due to inadvertent injury or removal of the parathyroid glands. Postoperative supplementation with oral calcium and vitamin D can be used to treat and prevent postoperative hypocalcemia.

References

https://t.me/USMLEWorldStep1

A 66-year-old man comes to the office to discuss his sexual health. He thinks that he has symptoms of low testosterone, similar to those described in an article he recently read in a health magazine. The patient has normal sexual desire but reduced spontaneous erections and reduced semen volume with ejaculation. He requires more stimulation to achieve a satisfactory erection and has a longer sexual refractory period than before. The patient has no known medical conditions and takes no medications. He does not use tobacco, alcohol, or illicit drugs. Vital signs are normal. BMI is 24.5 kg/m^2. Physical examination, including examination of the testes, is normal. After laboratory testing is completed, the physician finds no evidence of organic disease and concludes that the results are consistent with normal aging. Compared to a healthy young man, which of the following sets of test results would be most consistent with the physician's conclusion?

	Total testosterone	Free testosterone	Sex hormone–binding globulin
○ A.	Decreased	Decreased	Increased
○ B.	Decreased	Increased	Unchanged
○ C.	Decreased	Unchanged	Decreased
○ D.	Increased	Increased	Decreased
○ E.	Increased	Unchanged	Increased

Submit

https://t.me/USMLEWorldStep1

A 66-year-old man comes to the office to discuss his sexual health. He thinks that he has symptoms of low testosterone, similar to those described in an article he recently read in a health magazine. The patient has normal sexual desire but reduced spontaneous erections and reduced semen volume with ejaculation. He requires more stimulation to achieve a satisfactory erection and has a longer sexual refractory period than before. The patient has no known medical conditions and takes no medications. He does not use tobacco, alcohol, or illicit drugs. Vital signs are normal. BMI is 24.5 kg/m^2. Physical examination, including examination of the testes, is normal. After laboratory testing is completed, the physician finds no evidence of organic disease and concludes that the results are consistent with normal aging. Compared to a healthy young man, which of the following sets of test results would be most consistent with the physician's conclusion?

	Total testosterone	Free testosterone	Sex hormone–binding globulin	
✓ A.	Decreased	Decreased	Increased	(56%)
B.	Decreased	Increased	Unchanged	(3%)
C.	Decreased	Unchanged	Decreased	(36%)
D.	Increased	Increased	Decreased	(1%)
E.	Increased	Unchanged	Increased	(2%)

Correct

56%
Answered correctly

03 secs
Time Spent

2023
Version

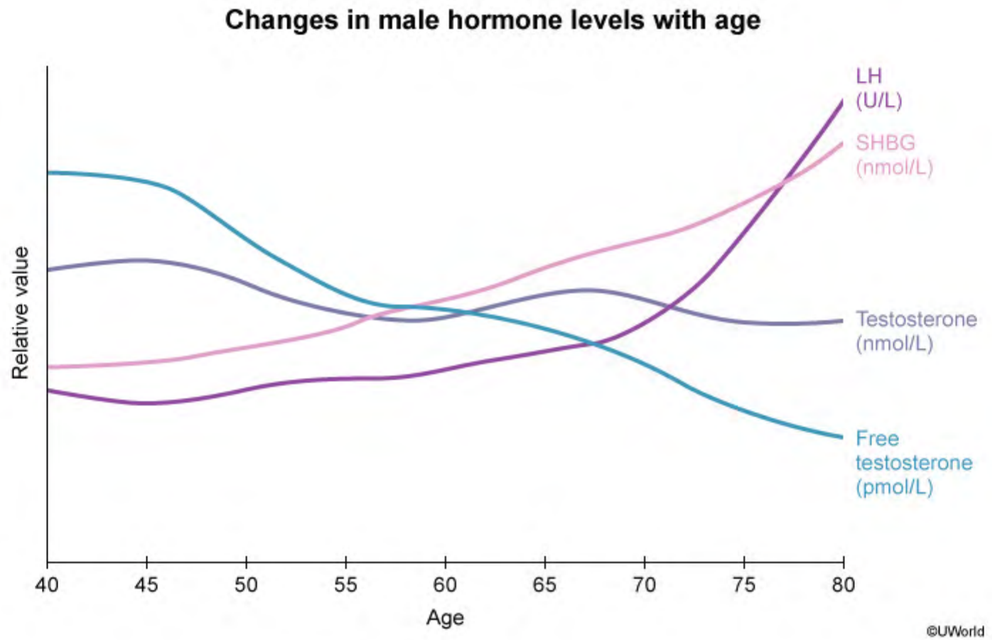
Explanation

Changes in male hormone levels with age

https://t.me/USMLEWorldStep1

Sex hormone–

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Free testosterone

https://t.me/USMLEWorldStep1

Unlike women, who typically experience a precipitous drop in sex hormone levels at menopause, men generally experience slower, more variable declines with aging. Typical findings seen in **normal aging** include the following:

- Slow decline in gonadal testosterone production with **lower total and free testosterone levels**
- A compensatory **rise in circulating LH levels**
- **Increased** hepatic synthesis (and rising serum levels) of **sex hormone–binding globulin** (SHBG)

Compared to women of similar age, men often report higher levels of sexual functioning, activity, and satisfaction as they age. However, men commonly experience mild, nonspecific changes in sexual function, including the following:

- **Decreased ejaculate volume**
- **Increased erectile latency** and sexual refractory period (ie, time from orgasm until another orgasm is possible)
- Moderately **impaired erectile function** with increased stimulation needed to achieve an erection

At very advanced age (eg, >80), very low testosterone levels can lead to specific hypogonadal symptoms (eg, loss of libido, erectile failure). However, this patient has nonspecific symptoms that are common in aging and do not suggest underlying gonadal failure.

(Choice B) Certain synthetic androgen analogues (eg, danazol) and progestins (eg, levonorgestrel) can displace testosterone from SHBG, increasing free testosterone without a significant change in SHBG levels. However, this pattern is not seen in normal aging.

(Choice C) SHBG levels are suppressed in patients with insulin resistance, diabetes, and obesity. If the pituitary-gonadal axis is intact, total testosterone levels are reduced, but free testosterone levels are relatively preserved. However, this patient has a normal weight, and SHBG is likely increased at age 66.

(Choice D) Testosterone suppresses SHBG synthesis. Excessive, unregulated testosterone (eg, exogenous androgen abuse) would usually be associated with low SHBG levels, but these values would not be seen in normal aging.

(Choice E) Hyperthyroidism often causes increased production of SHBG independent of age; total testosterone

https://t.me/USMLEWorldStep1

- **Increased erectile latency** and sexual refractory period (ie, time from orgasm until another orgasm is possible)
- Moderately **impaired erectile function** with increased stimulation needed to achieve an erection

At very advanced age (eg, >80), very low testosterone levels can lead to specific hypogonadal symptoms (eg, loss of libido, erectile failure). However, this patient has nonspecific symptoms that are common in aging and do not suggest underlying gonadal failure.

(Choice B) Certain synthetic androgen analogues (eg, danazol) and progestins (eg, levonorgestrel) can displace testosterone from SHBG, increasing free testosterone without a significant change in SHBG levels. However, this pattern is not seen in normal aging.

(Choice C) SHBG levels are suppressed in patients with insulin resistance, diabetes, and obesity. If the pituitary-gonadal axis is intact, total testosterone levels are reduced, but free testosterone levels are relatively preserved. However, this patient has a normal weight, and SHBG is likely increased at age 66.

(Choice D) Testosterone suppresses SHBG synthesis. Excessive, unregulated testosterone (eg, exogenous androgen abuse) would usually be associated with low SHBG levels, but these values would not be seen in normal aging.

(Choice E) Hyperthyroidism often causes increased production of SHBG independent of age; total testosterone increases to saturate the increased steroid hormone–binding sites, and free testosterone is unchanged. Although this patient likely has increased SHBG levels, his total and free testosterone levels are more likely decreased due to the effects of aging.

Educational objective:
Normal aging in men is associated with a slow decline in gonadal testosterone production, a compensatory rise in LH, and rising serum levels of sex hormone–binding globulin. Common, nonspecific symptoms include decreased ejaculate volume, increased erectile latency and sexual refractory time, and moderately impaired erectile function.

References

- Endocrinology of the aging male.

https://t.me/USMLEWorldStep1

A 14-year-old boy is brought to the office due to right breast enlargement. The patient says that he developed mild tenderness of the area 3 months ago and is distressed by its appearance. He is otherwise healthy and takes no daily medications. The patient does not use alcohol or recreational drugs. Height and weight are at the 80th and 60th percentile, respectively. Temperature is 36.7 C (98.1 F) and blood pressure is 112/62 mm Hg. Physical examination shows mild facial acne and the presence of hair on the upper lip and in the axillae. The right breast is enlarged with a 2-cm, firm, mildly tender mass under the nipple-areolar complex. There is no associated erythema or adenopathy. No palpable masses are present on the left. External genitalia are consistent with sexual maturity rating (Tanner stage) 4. The remainder of the examination is unremarkable. Which of the following is the best next step in management of this patient's condition?

- A. Obtain karyotype
- B. Obtain mammogram
- C. Obtain serum prolactin level
- D. Obtain serum testosterone level
- E. Provide reassurance

Submit

https://t.me/USMLEWorldStep1

A 14-year-old boy is brought to the office due to right breast enlargement. The patient says that he developed mild tenderness of the area 3 months ago and is distressed by its appearance. He is otherwise healthy and takes no daily medications. The patient does not use alcohol or recreational drugs. Height and weight are at the 80th and 60th percentile, respectively. Temperature is 36.7 C (98.1 F) and blood pressure is 112/62 mm Hg. Physical examination shows mild facial acne and the presence of hair on the upper lip and in the axillae. The right breast is enlarged with a 2-cm, firm, mildly tender mass under the nipple-areolar complex. There is no associated erythema or adenopathy. No palpable masses are present on the left. External genitalia are consistent with sexual maturity rating (Tanner stage) 4. The remainder of the examination is unremarkable. Which of the following is the best next step in management of this patient's condition?

- ✗ A. Obtain karyotype (5%)
- B. Obtain mammogram (23%)
- C. Obtain serum prolactin level (13%)
- D. Obtain serum testosterone level (8%)
- ✓ E. Provide reassurance (48%)

Incorrect
Correct answer
E

48%
Answered correctly

03 secs
Time Spent

2023
Version

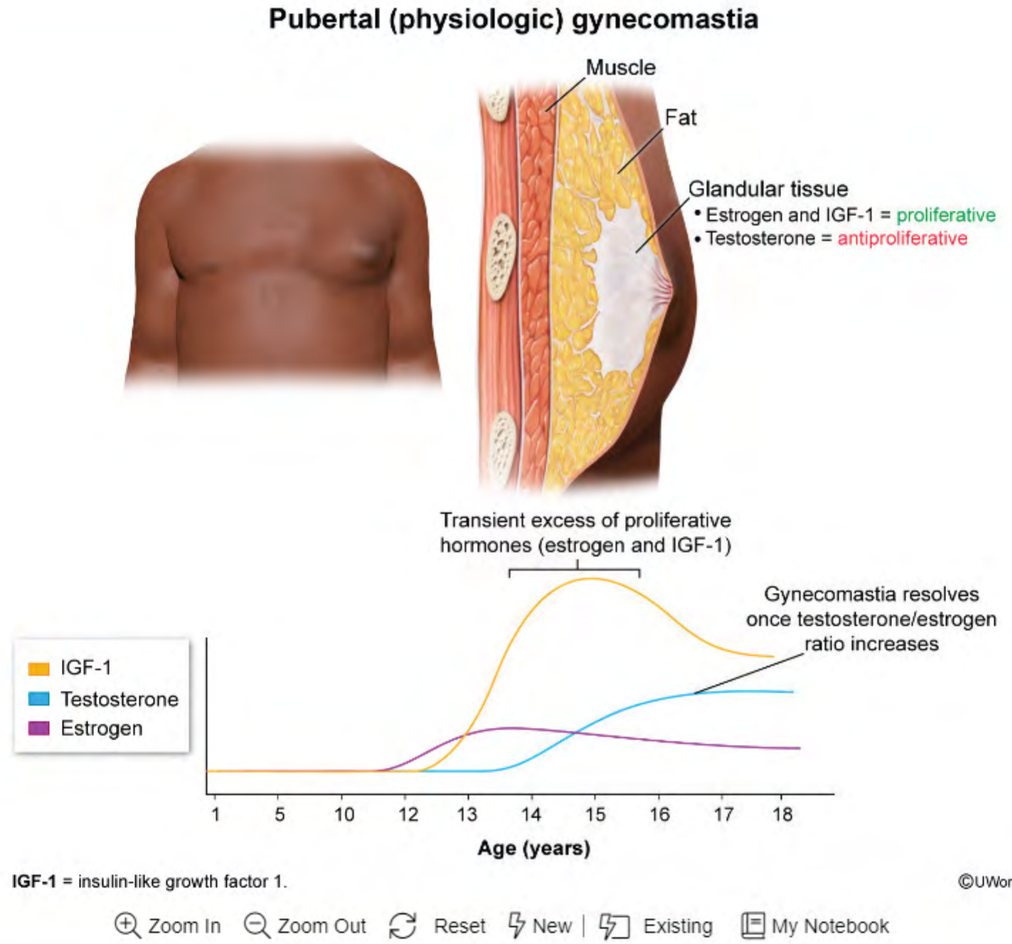
Explanation



https://t.me/USMLEWorldStep1

C. Obtain serum prolactin level (13%)

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

IGF-1 = insulin-like growth factor 1.

©UWorld

This adolescent most likely has **physiologic gynecomastia**, a benign condition affecting approximately half of boys during **midpuberty** (eg, sexual maturity ratings 2-4). Characteristic features include unilateral or bilateral breast enlargement that is directly under the nipple-areolar complex, is often **tender**, and measures <4 cm.

The mechanism of physiologic gynecomastia is likely multifactorial:

- **Imbalance of estradiol and testosterone:** During early male puberty, adrenal androgens increase (ie, adrenarche) and are converted by aromatase to estrogens, which stimulate growth of glandular breast tissue. Testosterone, which is produced by the testes and inhibits the development of breast tissue, typically remains low until full maturation of the hypothalamic-pituitary-gonadal axis. This may cause a transient estrogen excess, and some patients may be prone to gynecomastia because of a greater local concentration of aromatase.
- Higher insulin-like growth factor 1 (IGF-1) levels: Boys with physiologic gynecomastia have **higher serum IGF-1**, which stimulates glandular breast tissue, than those without, resulting in a further imbalance of prostimulatory hormones.

Diagnosis is clinical, but all adolescents should also be screened for substance use (eg, marijuana, alcohol, anabolic steroids), as was done in this patient, because it may contribute to gynecomastia. Management of physiologic gynecomastia includes observation and **reassurance** that it typically **self-resolves** within a year; frequent follow-up may be required for patients with psychosocial stress (eg, low self-esteem).

(Choices A, C, and D) Pathologic gynecomastia should be suspected in patients who develop breast tissue outside of midpuberty or who have rapidly enlarging tissue or tissue >4 cm. Evaluation may include a serum hormone panel (eg, hCG, LH, estradiol, testosterone) to evaluate for pathologic hormone imbalance. For example, low testosterone levels suggest hypogonadism and may warrant karyotyping to evaluate for Klinefelter syndrome (47,XXY) and/or serum prolactin to assess for a prolactin-secreting tumor. This patient's stage 4 pubic hair and otherwise normal examination make physiologic gynecomastia much more likely.

(Choice B) Mammography may be indicated for findings concerning for breast cancer, such as a fixed, nontender mass outside of the nipple-areolar complex with associated skin dimpling, nipple discharge, or adenopathy. Breast cancer is exceedingly rare in adolescent boys, and this patient has no red-flag findings.

https://t.me/USMLEWorldStep1

low until full maturation of the hypothalamic-pituitary-gonadal axis. This may cause a transient estrogen excess, and some patients may be prone to gynecomastia because of a greater local concentration of aromatase.

- Higher insulin-like growth factor 1 (IGF-1) levels: Boys with physiologic gynecomastia have **higher serum IGF-1**, which stimulates glandular breast tissue, than those without, resulting in a further imbalance of prostimulatory hormones.

Diagnosis is clinical, but all adolescents should also be screened for substance use (eg, marijuana, alcohol, anabolic steroids), as was done in this patient, because it may contribute to gynecomastia. Management of physiologic gynecomastia includes observation and **reassurance** that it typically **self-resolves** within a year; frequent follow-up may be required for patients with psychosocial stress (eg, low self-esteem).

(Choices A, C, and D) Pathologic gynecomastia should be suspected in patients who develop breast tissue outside of midpuberty or who have rapidly enlarging tissue or tissue >4 cm. Evaluation may include a serum hormone panel (eg, hCG, LH, estradiol, testosterone) to evaluate for pathologic hormone imbalance. For example, low testosterone levels suggest hypogonadism and may warrant karyotyping to evaluate for Klinefelter syndrome (47,XXY) and/or serum prolactin to assess for a prolactin-secreting tumor. This patient's stage 4 pubic hair and otherwise normal examination make physiologic gynecomastia much more likely.

(Choice B) Mammography may be indicated for findings concerning for breast cancer, such as a fixed, nontender mass outside of the nipple-areolar complex with associated skin dimpling, nipple discharge, or adenopathy. Breast cancer is exceedingly rare in adolescent boys, and this patient has no red-flag findings.

Educational objective:
Physiologic gynecomastia is a benign condition caused by a transient proestrogenic hormonal imbalance during midpuberty; it presents in adolescent boys with unilateral or bilateral tender breast enlargement. Patients should be reassured that the condition typically self-resolves within a year.

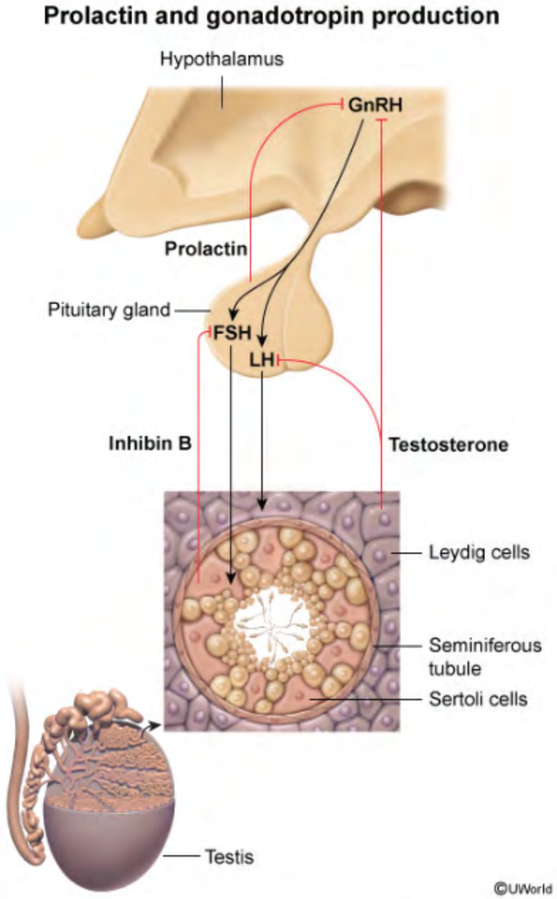
Pathophysiology	Endocrine, Diabetes & Metabolism	Gynecomastia
Subject	System	Topic

Copyright © UWorld. All rights reserved.

https://t.me/USMLEWorldStep1

IGF-1
Testosterone

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

This a
boys c
breast

The m

- In
  a
  T
  lo
  e
  a
- H
  IG
  p

Diagn
anabo
physic
freque

(Choi
outsid
hormone panel (eg, hCG, LH, estradiol, testosterone) to evaluate for pathologic hormone imbalance. For example, low testosterone levels suggest hypogonadism and may warrant karyotyping to evaluate for Klinefelter syndrome

https://t.me/USMLEWorldStep1

A 13-year-old boy is brought to the clinic due to breast development. Two months ago, the parents first noticed bilateral breast buds, which have slowly enlarged. Height is 151 cm (59.4 in) and weight is 37.5 kg (82.7 lb), corresponding to the 25th and 15th percentiles, respectively. BMI is at the 16th percentile. Temperature is 37 C (98.6 F), blood pressure is 106/64 mm Hg, pulse is 90/min, and respirations are 16/min. Breast palpation reveals bilateral concentric, mobile, tender mounds of tissue deep to the areolas, one measuring 1.5 cm in diameter and the other measuring 2.5 cm. Genital examination is consistent with sexual maturity rating (Tanner stage) 1. Which of the following clinical features in this patient is most concerning for a pathological cause of the breast enlargement?

- A. Bilateral presence
- B. Body mass index
- C. Breast tenderness
- D. Mass asymmetry
- E. Sexual maturity rating

Submit

https://t.me/USMLEWorldStep1

A 13-year-old boy is brought to the clinic due to breast development. Two months ago, the parents first noticed bilateral breast buds, which have slowly enlarged. Height is 151 cm (59.4 in) and weight is 37.5 kg (82.7 lb), corresponding to the 25th and 15th percentiles, respectively. BMI is at the 16th percentile. Temperature is 37 C (98.6 F), blood pressure is 106/64 mm Hg, pulse is 90/min, and respirations are 16/min. Breast palpation reveals bilateral concentric, mobile, tender mounds of tissue deep to the areolas, one measuring 1.5 cm in diameter and the other measuring 2.5 cm. Genital examination is consistent with sexual maturity rating (Tanner stage) 1. Which of the following clinical features in this patient is most concerning for a pathological cause of the breast enlargement?

- ✗ A. Bilateral presence (8%)
- B. Body mass index (10%)
- C. Breast tenderness (8%)
- D. Mass asymmetry (26%)
- ✓ E. Sexual maturity rating (46%)

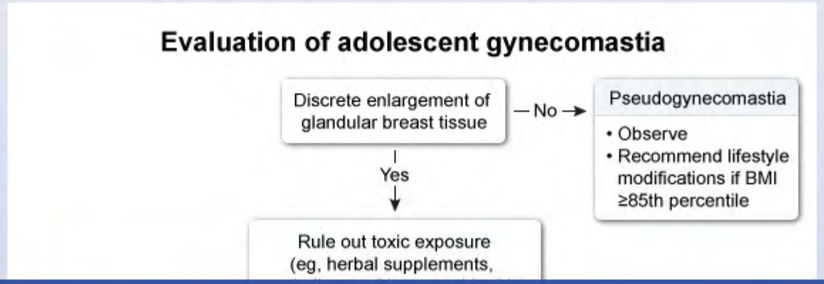
Incorrect
Correct answer
E

46%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

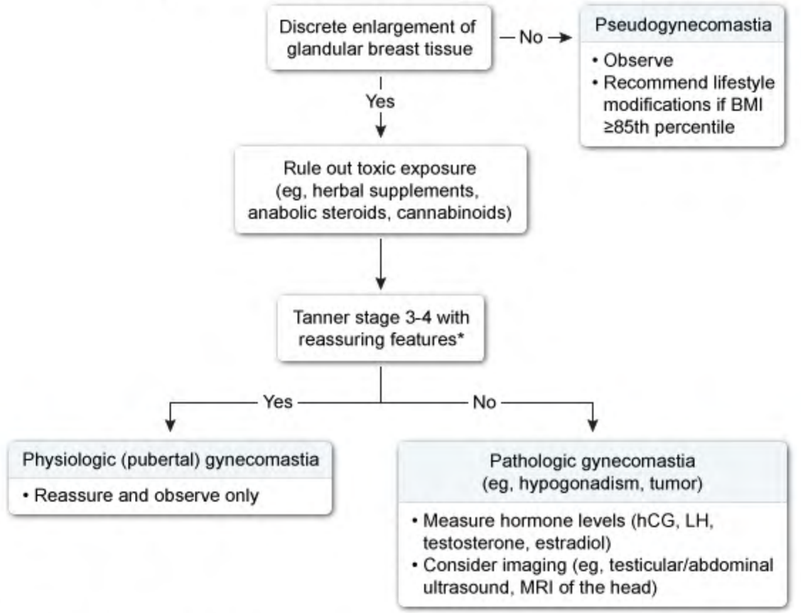


https://t.me/USMLEWorldStep1

A 13-year-old boy is brought to the clinic due to breast development. Two months ago, the parents first noticed
bilater
corres
(98.6 F
bilater
the oth
of the
enlarg

Exhibit Display

Evaluation of adolescent gynecomastia



*Not rapidly enlarging, <4 cm & otherwise normal examination.

©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Rule out toxic exposure
(eg, herbal supplements,

https://t.me/USMLEWorldStep1



This adolescent has **gynecomastia**, which can be physiologic (most common in this age group) or pathologic.

Physiologic (or pubertal) gynecomastia is caused by an imbalance of hormones that either stimulate or inhibit the development of breast tissue. During puberty in boys, androgens produced by the adrenal glands are peripherally aromatized to estrogens, providing a source of stimulatory hormones that are not yet counterbalanced by adult testosterone levels. This leads to physiologic development of breast tissue in over half of adolescent boys at Tanner stage 3-4 that can be unilateral or bilateral, asymmetric, and tender **(Choices A, C, and D)**. Physiologic gynecomastia is benign and typically resolves within a year.

In contrast, clinical features that raise concern for **pathologic** gynecomastia include:

- Development **before or after midpuberty** (eg, Tanner stage 1 or 5)
- **Rapid progression** or size >4 cm
- Location **eccentric to the nipple** areolar complex
- Persistence for >3 years

This patient has no testicular enlargement or signs of adrenarche (eg, axillary hair, body odor) and is therefore **prepubertal**, warranting further evaluation for a pathologic source of stimulatory hormones (eg, exogenous medications, testicular/adrenal/pituitary tumor).

(Choice B) Patients with elevated BMI are at risk for both pseudogynecomastia (fatty infiltration of the breast) as well as true gynecomastia due to increased activity of aromatase in obese males. This patient has a normal BMI.

Educational objective:
Adolescent gynecomastia is often physiologic due to an imbalance of estrogens and testosterone in early puberty. Features suggestive of pathologic gynecomastia include onset before or after midpuberty (eg, no secondary sexual characteristics), findings consistent with systemic illness (eg, goiter), as well as size >4 cm, rapid progression, and location eccentric to the nipple areolar complex.

References

https://t.me/USMLEWorldStep1

• Consider imaging (eg, testicular/abdominal ultrasound, MRI of the head)

Exhibit Display

This a

Physic
develc
aroma
testos
Tanne
gynec

In con

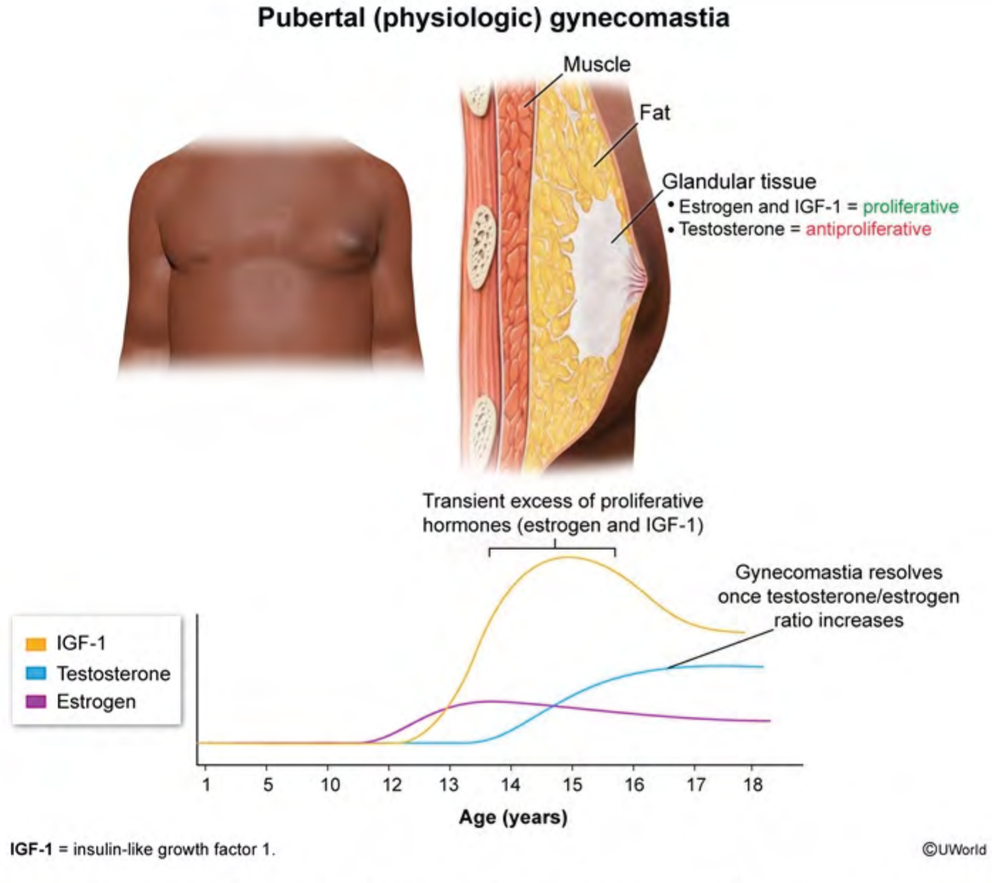
- D
- **R**
- L
- P

This p
prepu
medic

(Choi
well as

Educa
Adoles
Featur
charac
locatio

References



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

A 43-year-old woman comes to the office due to increasing fatigue and weight gain despite decreased food intake. She states, "I have not been feeling like myself lately." The patient asks to be referred to a dermatologist as she has always had "nice" skin that has now become dry. Her hair has been thinning and she hopes that a dermatologist can help with that too. Laboratory evaluation shows high serum TSH, low triiodothyronine (T3), and low thyroxine (T4) levels. The patient has a family member with fatigue whose energy level increased after liothyronine (T3) supplementation, and she asks to try this medication. Administering this therapy would most likely result in which of the following hormone level changes in this patient?

	TSH	T3	Reverse T3	T4
○ A.	No change	Increase	Increase	Decrease
○ B.	No change	Increase	Decrease	Decrease
○ C.	Decrease	Increase	Increase	Decrease
○ D.	Decrease	Increase	Decrease	Decrease
○ E.	Decrease	Increase	Decrease	Increase

Submit

https://t.me/USMLEWorldStep1

A 43-year-old woman comes to the office due to increasing fatigue and weight gain despite decreased food intake. She states, "I have not been feeling like myself lately." The patient asks to be referred to a dermatologist as she has always had "nice" skin that has now become dry. Her hair has been thinning and she hopes that a dermatologist can help with that too. Laboratory evaluation shows high serum TSH, low triiodothyronine (T3), and low thyroxine (T4) levels. The patient has a family member with fatigue whose energy level increased after liothyronine (T3) supplementation, and she asks to try this medication. Administering this therapy would most likely result in which of the following hormone level changes in this patient?

		TSH	T3	Reverse T3	T4	
	A.	No change	Increase	Increase	Decrease	(3%)
✗	B.	No change	Increase	Decrease	Decrease	(4%)
	C.	Decrease	Increase	Increase	Decrease	(26%)
✓	D.	Decrease	Increase	Decrease	Decrease	(48%)
	E.	Decrease	Increase	Decrease	Increase	(17%)

Incorrect
Correct answer
D

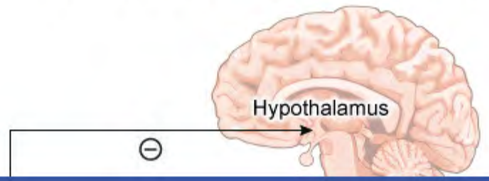
48%
Answered correctly

04 secs
Time Spent

2023
Version

Explanation

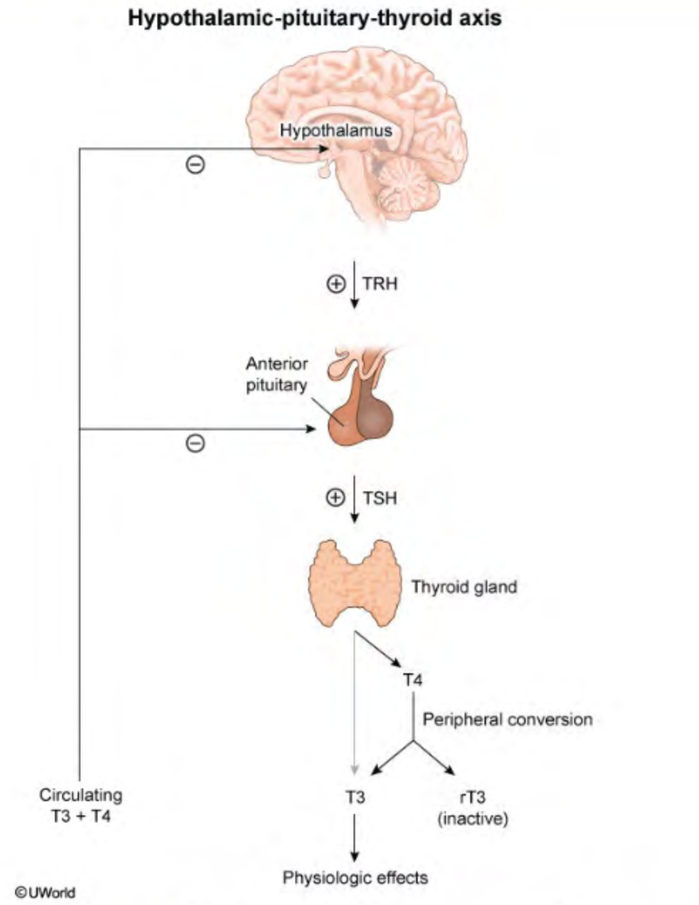
Hypothalamic-pituitary-thyroid axis



https://t.me/USMLEWorldStep1

result in which of the following hormone level changes in this patient?

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1



Circulating thyroid hormone exists in 3 primary forms:

1. **T4 (thyroxine)** is the major secretory product of the thyroid gland.
2. **T3 (triiodothyronine)** is the most active form of thyroid hormone; a small amount is released by the thyroid gland, but the majority arises from peripheral deiodination of T4.
3. **Reverse T3 (rT3)** is an inactive form that is generated almost entirely from the peripheral conversion of T4.

The hypothalamus-pituitary-thyroid axis is regulated via **negative feedback** by thyroid hormone on thyrotropin-releasing hormone–secreting neurons in the hypothalamus and thyrotrophs of the anterior pituitary. In the normal state, most of the circulating thyroid hormone is in the form of T4, which provides most of the feedback suppression of TSH release. However, T3 also suppresses TSH.

This patient has primary hypothyroidism, with low thyroid hormone (T3 and T4) and elevated TSH levels. Exogenous T3 supplementation **rapidly suppresses TSH** levels by increasing negative feedback, which in turn decreases T4 secretion from the thyroid gland. Furthermore, rT3 also decreases because less T4 is available for conversion (T3 cannot be converted into rT3).

However, synthetic T3 (liothyronine) is not recommended for the routine treatment of hypothyroidism, as it has a short half-life and patients can experience wide fluctuations in plasma T3 levels. T4 (levothyroxine) supplementation provides a more physiologic effect and is preferred.

Educational objective:
TSH from the anterior pituitary stimulates the thyroid to produce thyroxine (T4) and a small amount of triiodothyronine (T3). T4 is converted in peripheral tissues to T3 (active form) and reverse T3 (inactive form). TSH secretion is under negative feedback by thyroid hormone on the hypothalamus and pituitary.

References

- Mini review: thyrotropin-releasing hormone and the thyroid hormone feedback mechanism.

Physiology Endocrine, Diabetes & Metabolism Hypothyroidism

https://t.me/USMLEWorldStep1

A 43-year-old woman comes to the office due to episodic confusion, blurred vision, tremors, and sweating. The episodes have increased in intensity in the past few months and seem to occur any time during the day. Her symptoms are relieved by drinking orange juice. During a recent episode, the patient's blood glucose level was 32 mg/dL as measured by her husband's home glucose meter. Medical history includes major depression and irritable bowel syndrome. Laboratory studies performed during the next episode of symptoms show the following results:

Glucose	35 mg/dL	
Insulin	18 µU/mL	(normal: <3 µU/mL)
C-peptide	4.01 ng/mL	(normal: <0.6ng/mL)

Which of the following is the most likely cause of this patient's symptoms?

- A. Alpha cell tumor
- B. Insulin administration
- C. Somatostatinoma
- D. Sulfonylurea use
- E. VIP-secreting tumor

Submit

https://t.me/USMLEWorldStep1

A 43-year-old woman comes to the office due to episodic confusion, blurred vision, tremors, and sweating. The episodes have increased in intensity in the past few months and seem to occur any time during the day. Her symptoms are relieved by drinking orange juice. During a recent episode, the patient's blood glucose level was 32 mg/dL as measured by her husband's home glucose meter. Medical history includes major depression and irritable bowel syndrome. Laboratory studies performed during the next episode of symptoms show the following results:

Glucose	35 mg/dL	
Insulin	18 µU/mL	(normal: <3 µU/mL)
C-peptide	4.01 ng/mL	(normal: <0.6ng/mL)

Which of the following is the most likely cause of this patient's symptoms?

- A. Alpha cell tumor (5%)
- ✗ B. Insulin administration (7%)
- C. Somatostatinoma (5%)
- ✓ D. Sulfonylurea use (72%)
- E. VIP-secreting tumor (8%)

Incorrect
Correct answer
D

72%
Answered correctly

04 secs
Time Spent

2023
Version

Explanation

Evaluation of hypoglycemia			
	Serum insulin	C-peptide	Hypoglycemic drug assay

https://t.me/USMLEWorldStep1

Evaluation of hypoglycemia			
	Serum insulin	**C-peptide**	**Hypoglycemic drug assay**
Exogenous insulin	Normal/increased	**Low**	Negative
Oral hypoglycemic agents	Normal/increased	Normal/elevated	**Positive**
Insulinoma	Normal/increased	Normal/elevated	Negative

This patient has symptomatic **hypoglycemia**, confirmed by the **Whipple triad**:

- Symptoms consistent with hypoglycemia (eg, tremor, diaphoresis, confusion)
- Low blood glucose level
- Relief of hypoglycemic symptoms when the blood glucose level is corrected

Insulin is initially synthesized as preproinsulin, after which the signal peptide is removed, yielding proinsulin. In the secretory granules, proinsulin is cleaved into **insulin** and **C-peptide**, which are then released together in equimolar amounts. Normally, as blood glucose falls, endogenous insulin secretion is suppressed, and serum levels of both insulin and C-peptide drop.

Hypoglycemia due to excessive **endogenous insulin production** is associated with **elevated levels of C-peptide**. This can occur due to autonomous insulin-producing tumors (insulinomas) or intake of insulin secretagogues (eg, **sulfonylureas**). Self-induced hypoglycemia via oral hypoglycemics is often a manifestation of a factitious disorder and is typically seen in health care workers and family members of patients with diabetes using these medications (which is likely in this patient whose husband has home glucose-testing supplies). Sulfonylurea abuse can be confirmed by testing the urine or blood for specific hypoglycemic agents.

(Choice A) Glucagonoma is a rare tumor of pancreatic alpha cells that secretes excessive amounts of glucagon. This results in hyperglycemia, weight loss, anemia, and necrolytic migratory erythema (a raised, erythematous rash

https://t.me/USMLEWorldStep1

secretory granules, proinsulin is cleaved into **insulin** and **C-peptide**, which are then released together in equimolar amounts. Normally, as blood glucose falls, endogenous insulin secretion is suppressed, and serum levels of both insulin and C-peptide drop.

Hypoglycemia due to excessive **endogenous insulin production** is associated with **elevated levels of C-peptide**. This can occur due to autonomous insulin-producing tumors (insulinomas) or intake of insulin secretagogues (eg, **sulfonylureas**). Self-induced hypoglycemia via oral hypoglycemics is often a manifestation of a factitious disorder and is typically seen in health care workers and family members of patients with diabetes using these medications (which is likely in this patient whose husband has home glucose-testing supplies). Sulfonylurea abuse can be confirmed by testing the urine or blood for specific hypoglycemic agents.

(Choice A) Glucagonoma is a rare tumor of pancreatic alpha cells that secretes excessive amounts of glucagon. This results in hyperglycemia, weight loss, anemia, and necrolytic migratory erythema (a raised, erythematous rash affecting the face, groin, and extremities).

(Choice B) Hypoglycemia due to exogenous insulin injection, which does not contain C-peptide, is associated with an elevated serum insulin level but an undetectable C-peptide level.

(Choice C) Somatostatinoma is a rare tumor of pancreatic delta cells that is associated with hyperglycemia, weight loss, abdominal pain, steatorrhea, cholelithiasis, and hypochlorhydria. These manifestations are due to somatostatin-induced inhibition of insulin, gastrin, secretin, and cholecystokinin secretion, as well as decreased gastrointestinal motility.

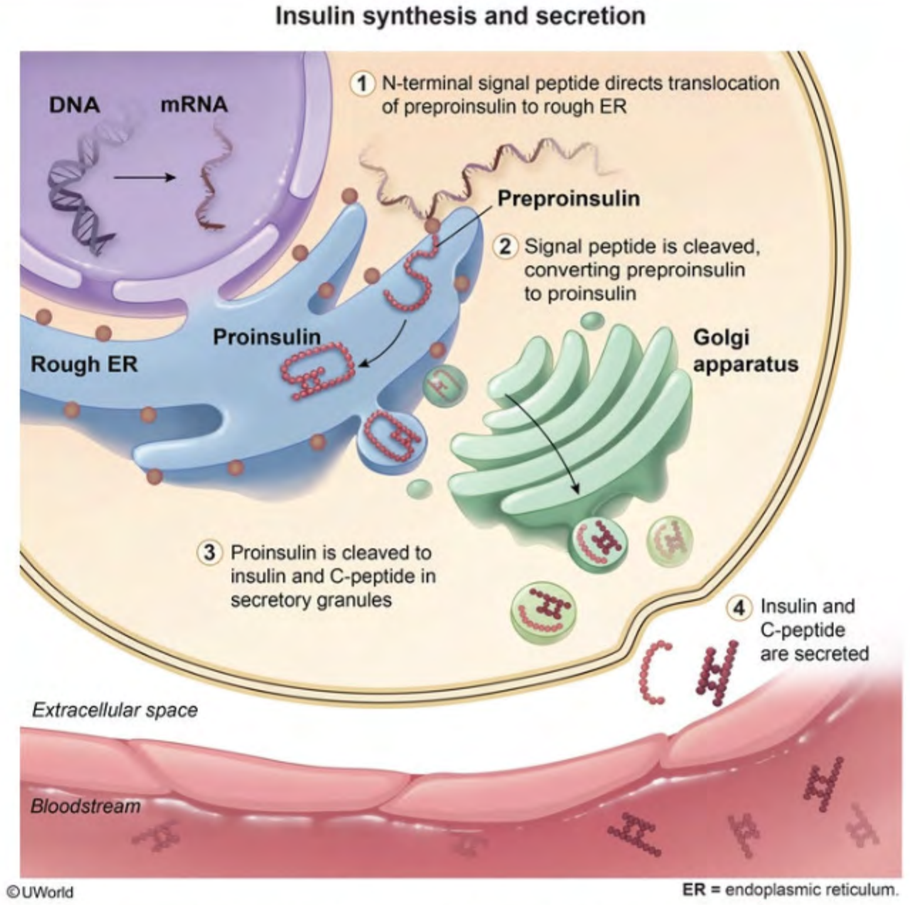
(Choice E) VIPomas are non–beta cell pancreatic islet cell tumors that hypersecrete vasoactive intestinal polypeptide (VIP). Features include watery diarrhea, hypokalemia, and impaired gastric acid secretion.

Educational objective:
Hypoglycemia is characterized by tremor, diaphoresis, and confusion in association with a low blood glucose level and resolution of symptoms when the blood glucose level is corrected. Hypoglycemia with elevated insulin and low C-peptide levels suggests exogenous insulin injection, whereas elevated C-peptide suggests an insulin secretagogue or insulin-secreting tumor.

References

https://t.me/USMLEWorldStep1

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

This p

- S
- L
- R

Insulin
secret
amour
insulin

Hypog
peptic
secret
a facti
using
Sulfon

(Choi

This results in hyperglycemia, weight loss, anemia, and necrolytic migratory erythema (a raised, erythematous rash

https://t.me/USMLEWorldStep1

A 2-year-old boy is brought to the office by his parents. He is currently toilet-training during the day and at nighttime. After he urinated in the toilet last night, his parents forgot to flush the toilet and noticed that the boy's urine turned black overnight. The child has no significant past medical history and takes no medications. He can say 2-word sentences, follow 2-step directions, and jump with 2 feet off the ground. Examination shows a well-nourished child with no swelling or tenderness of any joints. Urinalysis results are as follows:

Color	black
Specific gravity	1.022
Protein	none
Blood	negative
Glucose	negative
Ketones	negative
Leukocyte esterase	negative

Which of the following conversion pathways is most likely deficient in this patient?

- A. Leucine to acetoacetate
- B. Phenylalanine to tyrosine
- C. Serine to cysteine
- D. Tyrosine to fumarate
- E. Valine to glutamic acid

Submit

https://t.me/USMLEWorldStep1

A 2-year-old boy is brought to the office by his parents. He is currently toilet-training during the day and at nighttime. After he urinated in the toilet last night, his parents forgot to flush the toilet and noticed that the boy's urine turned black overnight. The child has no significant past medical history and takes no medications. He can say 2-word sentences, follow 2-step directions, and jump with 2 feet off the ground. Examination shows a well-nourished child with no swelling or tenderness of any joints. Urinalysis results are as follows:

Color	black
Specific gravity	1.022
Protein	none
Blood	negative
Glucose	negative
Ketones	negative
Leukocyte esterase	negative

Which of the following conversion pathways is most likely deficient in this patient?

- ✗ A. Leucine to acetoacetate (6%)
- B. Phenylalanine to tyrosine (19%)
- C. Serine to cysteine (15%)
- ✓ D. Tyrosine to fumarate (54%)
- E. Valine to glutamic acid (3%)

Incorrect
Correct answer
D

54%
Answered correctly

04 secs
Time Spent

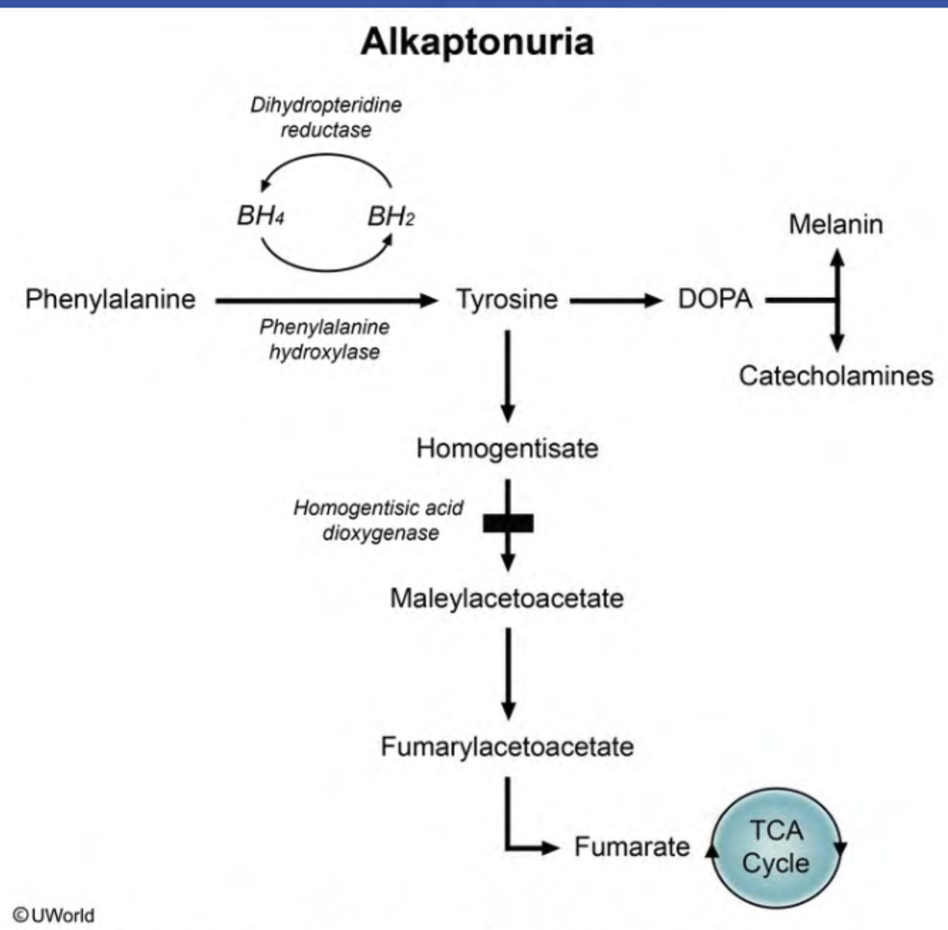
2023
Version

Explanation

https://t.me/USMLEWorldStep1

C. Serine to cysteine (15%)

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Alkaptonuria is an **autosomal recessive** disorder of **tyrosine metabolism**. Deficiency of homogentisic acid dioxygenase blocks homogentisic acid metabolism, preventing the conversion of tyrosine to fumarate. Homogentisic acid accumulates in the body and is excreted in the urine, imparting a **black color** to the **urine** if allowed to sit and undergo oxidation. In patients with alkaptonuria, the retained homogentisic acid selectively binds to collagen in connective tissues, tendons, and cartilage. This leads to "**ochronosis**," a blue-black pigmentation most evident in the ears, nose, and cheeks, and **ochronotic arthropathy**, which typically manifests during adulthood.

(Choice A) Leucine is a branched-chain amino acid that is elevated in maple syrup urine disease. Isoleucine and valine are also increased. Impaired metabolism of these amino acids leads to cerebral edema, seizures, and a sweet smell of the urine.

(Choice B) Conversion of phenylalanine to tyrosine is defective in phenylketonuria and usually occurs due to a defect in phenylalanine hydroxylase. Undiagnosed and untreated phenylketonuria results in significant intellectual disability not seen in this patient.

(Choice C) Impaired renal cystine (a homodimer of cysteine) transport leads to cystinuria, a disease characterized by flank pain, hematuria, and renal stones in childhood or adolescence.

(Choice E) Sickle cell anemia results from the substitution of valine for glutamic acid due to a single-nucleotide polymorphism. This mutation leads to loss of red cell elasticity, polymerization of sickle hemoglobin, and sickling of red blood cells, which results in vasoocclusive crises.

Educational objective:
Alkaptonuria is an autosomal recessive disorder in which the lack of homogentisic acid dioxygenase blocks the metabolism of tyrosine, leading to an accumulation of homogentisic acid. Clinical features include a black urine color when exposed to air, a blue-black pigmentation on the face, and ochronotic arthropathy.

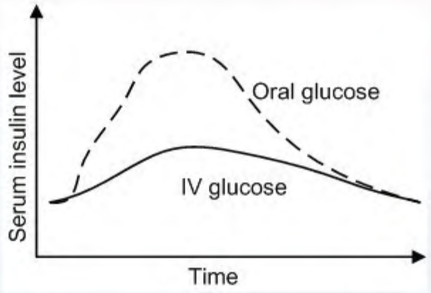
References

- Alkaptonuria.

Biochemistry	Endocrine, Diabetes & Metabolism	Alkaptonuria
Subject	System	Topic

https://t.me/USMLEWorldStep1

Researchers measure the serum insulin levels of healthy volunteers after equivalent loads of oral and intravenous glucose. The following curves are observed:



Which of the following endogenous substances best explains the difference between the curves?

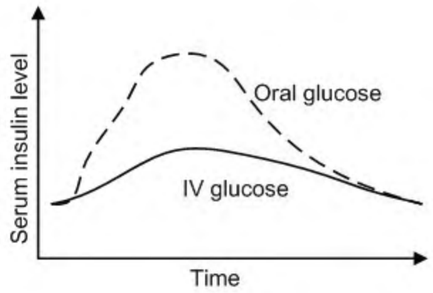
- A. Insulin-like growth factor-1
- B. Glucagon-like peptide-1
- C. Somatostatin
- D. Secretin
- E. Cholecystokinin

Submit

https://t.me/USMLEWorldStep1

Researchers measure the serum insulin levels of healthy volunteers after equivalent loads of oral and intravenous glucos

Exhibit Display



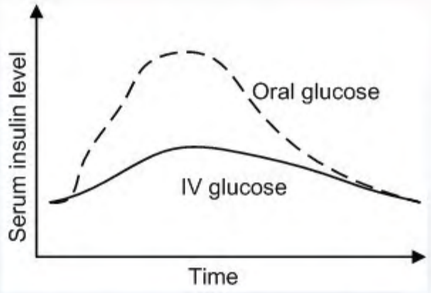
Zoom In Zoom Out Reset New | Existing My Notebook

Which

Sub

https://t.me/USMLEWorldStep1

Researchers measure the serum insulin levels of healthy volunteers after equivalent loads of oral and intravenous glucose. The following curves are observed:



Which of the following endogenous substances best explains the difference between the curves?

- ✗ A. Insulin-like growth factor-1 (19%)
- ✓ B. Glucagon-like peptide-1 (51%)
- C. Somatostatin (10%)
- D. Secretin (12%)
- E. Cholecystokinin (6%)

Incorrect
Correct answer
B

51%
Answered correctly

08 secs
Time Spent

2023
Version

Explanation

Incretins are gastrointestinal hormones produced by the gut mucosa that stimulate pancreatic insulin secretion in response to sugar-containing meals. This response is independent of blood glucose levels, and typically occurs prior to any elevation in blood glucose level following a meal. Two hormones with incretin effects are glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide (glucose-dependent insulinotropic peptide, GIP). Insulin levels will

https://t.me/USMLEWorldStep1

Incretins are gastrointestinal hormones produced by the gut mucosa that stimulate pancreatic insulin secretion in response to sugar-containing meals. This response is independent of blood glucose levels, and typically occurs prior to any elevation in blood glucose level following a meal. Two hormones with incretin effects are glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide (glucose-dependent insulinotropic peptide, GIP). Insulin levels will also increase following intravenous administration of glucose due to the sensitivity of the pancreatic beta-cells to increases in blood glucose, but this increase will not be as marked as that seen following oral glucose administration because the effect of incretin is absent.

(Choice A) Insulin-like growth factor-1 is produced by the liver in response to stimulation by growth hormone. It functions as a mitogen and as an inhibitor of apoptosis.

(Choice C) Somatostatin is produced by cells in the stomach, small bowel and pancreas and inhibits the production and release of most other gastrointestinal hormones, including insulin.

(Choice D) Secretin is a hormone produced in the duodenum in response to increased luminal acidity. It stimulates the release of bicarbonate-rich secretions from the pancreas, gallbladder and duodenum. It also increases the activity of cholecystokinin.

(Choice E) Cholecystokinin is produced by the duodenum in response to a fat or protein-rich meal. It has many functions including inhibition of further gastric emptying, stimulation of pancreatic enzyme secretion and stimulation of bile production and gallbladder contraction.

Educational objective:
Incretin functions by stimulating insulin release following oral consumption of glucose. Incretin-stimulated insulin release is independent of the increase in insulin secretion brought on by elevations in the blood glucose level.

Physiology	Endocrine, Diabetes & Metabolism	Diabetes mellitus
Subject	System	Topic

https://t.me/USMLEWorldStep1

A 46-year-old man comes to the office to follow up mixed hyperlipidemia. His lipid levels have progressively worsened over the last 10 years associated with gradual weight gain. In the last 6 months, the patient has attempted to modify his diet and exercise regimen, but his lipid levels have not improved. Past medical history is unremarkable, and he currently takes no medications. The patient does not use tobacco, alcohol, or illicit drugs. Blood pressure is 130/86 mm Hg, pulse is 76/min, and BMI is 28 kg/m^2. Cardiovascular examination is normal. Which of the following drugs, when used as monotherapy, would be most likely to increase triglyceride levels in this patient?

- A. Atorvastatin
- B. Cholestyramine
- C. Ezetimibe
- D. Gemfibrozil
- E. Niacin

Submit

https://t.me/USMLEWorldStep1

A 46-year-old man comes to the office to follow up mixed hyperlipidemia. His lipid levels have progressively worsened over the last 10 years associated with gradual weight gain. In the last 6 months, the patient has attempted to modify his diet and exercise regimen, but his lipid levels have not improved. Past medical history is unremarkable, and he currently takes no medications. The patient does not use tobacco, alcohol, or illicit drugs. Blood pressure is 130/86 mm Hg, pulse is 76/min, and BMI is 28 kg/m^2. Cardiovascular examination is normal. Which of the following drugs, when used as monotherapy, would be most likely to increase triglyceride levels in this patient?

- ✗ A. Atorvastatin (6%)
- ✓ B. Cholestyramine (47%)
- C. Ezetimibe (13%)
- D. Gemfibrozil (16%)
- E. Niacin (15%)

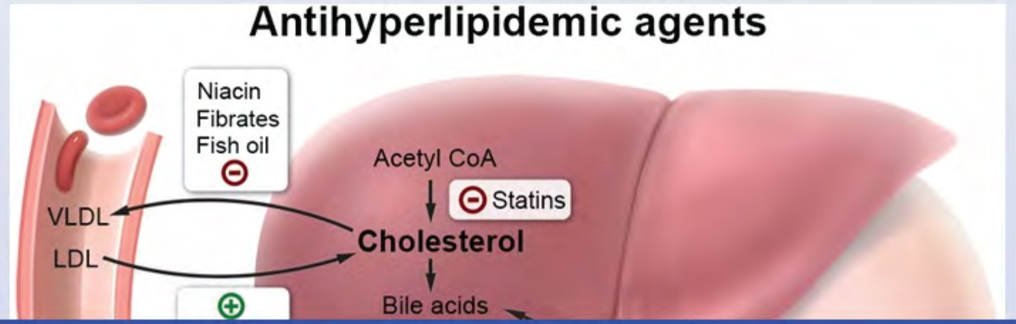
Incorrect
Correct answer
B

47%
Answered correctly

04 secs
Time Spent

2023
Version

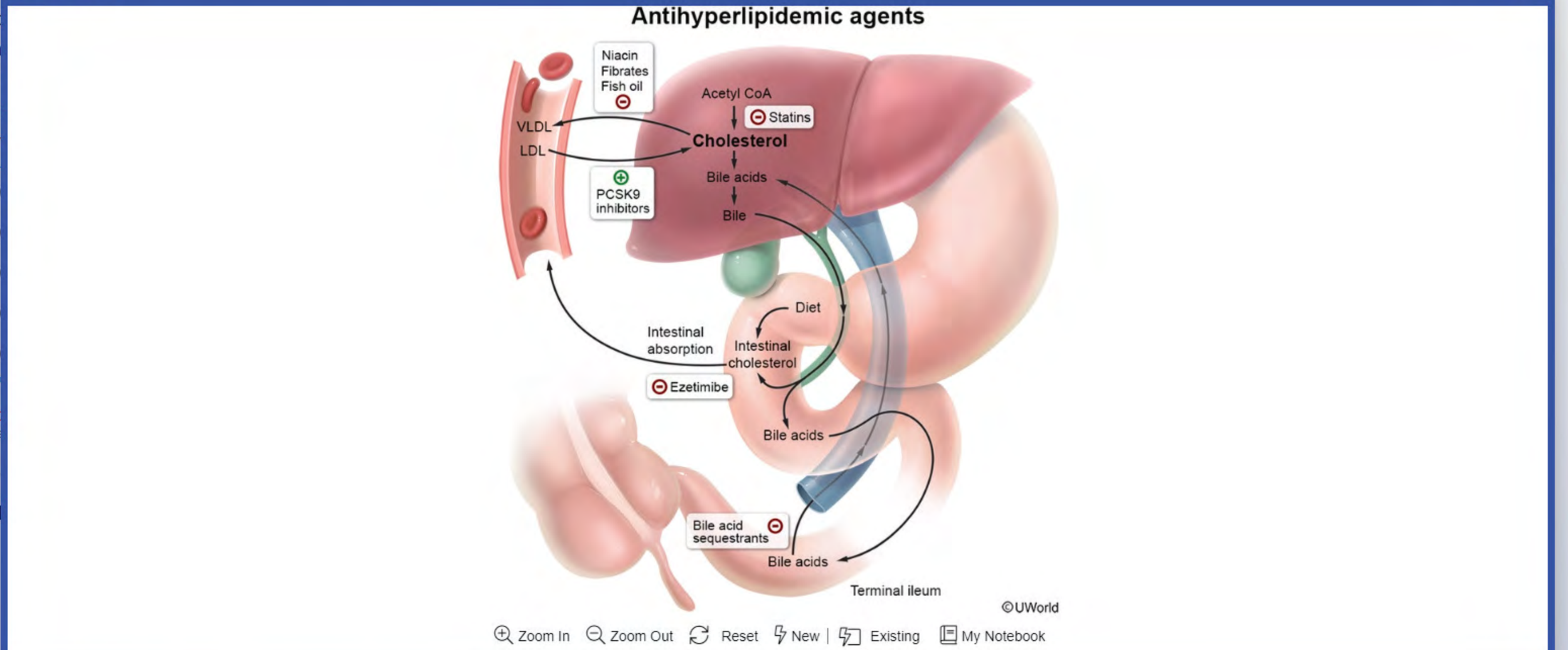
Explanation

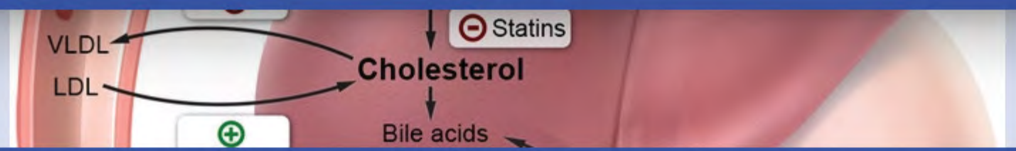


https://t.me/USMLEWorldStep1

A 46-year-old man comes to the office to follow up mixed hyperlipidemia. His lipid levels have progressively worse
attemp
unrem
Blood
Which
patien

Exhibit Display





https://t.me/USMLEWorldStep1



Bile acid-binding resins (eg, cholestyramine, colestipol, colesevelam) work by binding bile acids in the gastrointestinal tract, inhibiting **enterohepatic circulation**. This leads to diversion of hepatic cholesterol to synthesis of new bile acids, increased uptake of LDL cholesterol from the circulation, and reduced blood LDL levels.

The main side effects of bile acid-binding resins are gastrointestinal upset and impaired absorption of nutrients and drugs. In addition, bile acid-binding resins increase hepatic production of triglycerides and increase the release of triglyceride-heavy VLDL particles into the circulation, leading to **hypertriglyceridemia**.

(Choice A) Statins cause modest reductions in triglyceride levels by decreasing synthesis and increasing clearance of VLDL particles.

(Choice C) Ezetimibe selectively inhibits the intestinal absorption of cholesterol and lowers LDL levels. Ezetimibe does not affect triglyceride absorption but may lower blood triglyceride levels slightly.

(Choice D) Fibrates (eg, gemfibrozil, fenofibrate) inhibit hepatic production of triglycerides and are first-line treatments for hypertriglyceridemia.

(Choice E) Niacin reduces blood triglyceride levels, raises HDL levels, and decreases VLDL conversion to LDL, thereby decreasing LDL concentrations as well.

Educational objective:
Bile acid-binding resins inhibit the enterohepatic circulation of bile acids. This leads to diversion of hepatic cholesterol to synthesis of new bile acids, increased uptake of cholesterol from the circulation, and reduced blood LDL levels. However, bile acid-binding resins increase hepatic production of triglycerides and can cause hypertriglyceridemia.

Pharmacology	Endocrine, Diabetes & Metabolism	Dyslipidemia
Subject	System	Topic

Copyright © UWorld. All rights reserved.

https://t.me/USMLEWorldStep1

A 17-year-old boy who was recently diagnosed with type 1 diabetes mellitus is found unresponsive at home. His family reports that the patient did not feel good last night and skipped dinner, but he still took his usual dose of insulin. Paramedics find that his fingerstick blood glucose is 32 mg/dL and immediately administer intramuscular glucagon. Glucagon binds to a transmembrane receptor in hepatocytes, which promotes binding of intracellular GTP to a specific receptor-associated protein. This leads to further downstream signaling and rapid metabolic changes within hepatocytes, including a rapid decrease in intracellular glycogen stores and release of glucose into the blood. Which of the following is the most likely mediator responsible for these effects?

- A. cGMP-dependent protein kinase
- B. Janus tyrosine kinase
- C. Phosphodiesterase
- D. Protein kinase A
- E. Tyrosine-specific protein kinase

Submit

https://t.me/USMLEWorldStep1

A 17-year-old boy who was recently diagnosed with type 1 diabetes mellitus is found unresponsive at home. His family reports that the patient did not feel good last night and skipped dinner, but he still took his usual dose of insulin. Paramedics find that his fingerstick blood glucose is 32 mg/dL and immediately administer intramuscular glucagon. Glucagon binds to a transmembrane receptor in hepatocytes, which promotes binding of intracellular GTP to a specific receptor-associated protein. This leads to further downstream signaling and rapid metabolic changes within hepatocytes, including a rapid decrease in intracellular glycogen stores and release of glucose into the blood. Which of the following is the most likely mediator responsible for these effects?

- A. cGMP-dependent protein kinase (18%)
- ✕ B. Janus tyrosine kinase (6%)
- C. Phosphodiesterase (3%)
- ✓ D. Protein kinase A (61%)
- E. Tyrosine-specific protein kinase (10%)

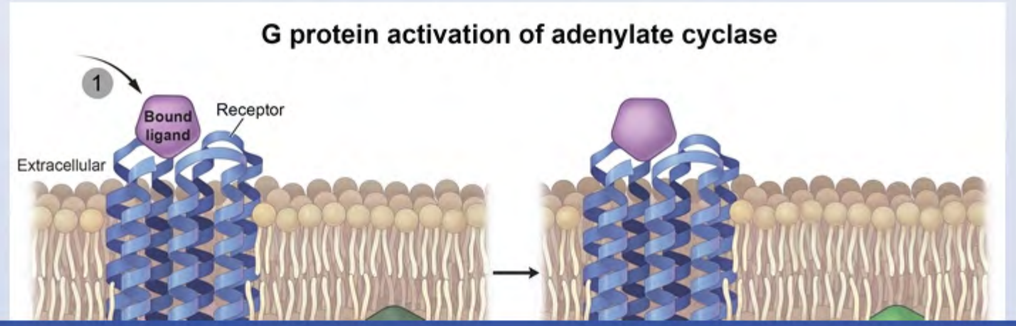
Incorrect
Correct answer
D

61%
Answered correctly

04 secs
Time Spent

2023
Version

Explanation



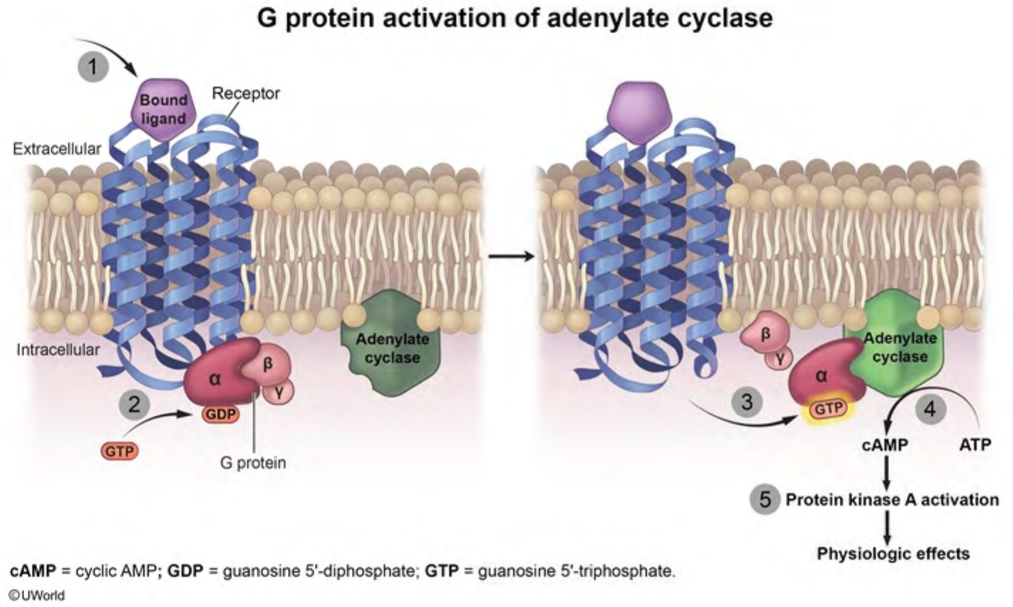
https://t.me/USMLEWorldStep1

A 17-year-old boy who was recently diagnosed with type 1 diabetes mellitus is found unresponsive at home. His family
insulin
glucag
GTP t
chang
the blo

Incc
Corre
D

Expl

Exhibit Display

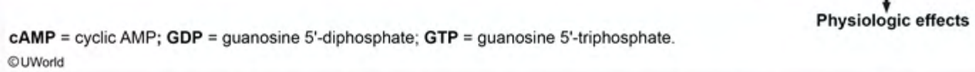


cAMP = cyclic AMP; **GDP** = guanosine 5'-diphosphate; **GTP** = guanosine 5'-triphosphate.

©UWorld

Zoom In Zoom Out Reset New | Existing My Notebook

https://t.me/USMLEWorldStep1



cAMP = cyclic AMP; **GDP** = guanosine 5'-diphosphate; **GTP** = guanosine 5'-triphosphate.
©UWorld

Glucagon exerts its effects through G protein-coupled receptors using the **adenylate cyclase second messenger system**. G protein is a heterotrimer consisting of alpha, beta, and gamma subunits associated with the intracellular domain of these transmembrane receptors. The alpha subunit of the inactivated G protein is bound to GDP. On **receptor activation**, the alpha subunit undergoes a conformational change, which releases GDP and binds GTP. **GTP binding** allows the alpha subunit to dissociate from the remainder of the G protein complex.

There are multiple subtypes of alpha G proteins, each with different secondary effects. A specific alpha subunit known as **G_s** (present in glucagon, TSH, and PTH receptor complexes) **activates adenylate cyclase** when released from the G protein complex. Adenylate cyclase converts ATP to **cAMP**, which activates **protein kinase A**. Protein kinase A phosphorylates specific serine/threonine residues in various enzymes, leading to their activation or deactivation. Protein kinase A also phosphorylates proteins that bind to the regulatory regions of genes on DNA.

(Choice A) cGMP activates protein kinase G, which mediates a number of intracellular effects (eg, smooth muscle relaxation, platelet activation, sperm metabolism). cGMP is inactivated by cGMP phosphodiesterase, which cleaves cGMP in the corpus cavernosum of the penis and regulates penile erection. Drugs that inhibit cGMP-specific phosphodiesterase (eg, sildenafil) are used in the treatment of erectile dysfunction.

(Choice B) Janus tyrosine kinase (JAK) is a cytoplasmic protein activated by ligand binding to non-G protein-coupled transmembrane receptors that lack intrinsic tyrosine kinase activity. Growth hormone, erythropoietin, and cytokines (eg, interferon) are common ligands for these receptors. JAKs activate cytoplasmic transcription factors called STATs (signal transducers and activators of transcription), which enter the nucleus to promote gene transcription.

(Choice C) cAMP is cleaved by the enzyme cAMP phosphodiesterase to its inactive form, 5'-AMP. Drugs that inhibit cAMP phosphodiesterase lead to prolongation of the actions of cAMP. An example is the use of theophylline in bronchial asthma.

(Choice E) Ligands such as insulin and epidermal growth factor act through transmembrane receptors that have

https://t.me/USMLEWorldStep1

binds GTP. **GTP binding** allows the alpha subunit to dissociate from the remainder of the G protein complex.

There are multiple subtypes of alpha G proteins, each with different secondary effects. A specific alpha subunit known as $\mathbf{G_s}$ (present in glucagon, TSH, and PTH receptor complexes) **activates adenylate cyclase** when released from the G protein complex. Adenylate cyclase converts ATP to **cAMP**, which activates **protein kinase A**. Protein kinase A phosphorylates specific serine/threonine residues in various enzymes, leading to their activation or deactivation. Protein kinase A also phosphorylates proteins that bind to the regulatory regions of genes on DNA.

(Choice A) cGMP activates protein kinase G, which mediates a number of intracellular effects (eg, smooth muscle relaxation, platelet activation, sperm metabolism). cGMP is inactivated by cGMP phosphodiesterase, which cleaves cGMP in the corpus cavernosum of the penis and regulates penile erection. Drugs that inhibit cGMP-specific phosphodiesterase (eg, sildenafil) are used in the treatment of erectile dysfunction.

(Choice B) Janus tyrosine kinase (JAK) is a cytoplasmic protein activated by ligand binding to non-G protein-coupled transmembrane receptors that lack intrinsic tyrosine kinase activity. Growth hormone, erythropoietin, and cytokines (eg, interferon) are common ligands for these receptors. JAKs activate cytoplasmic transcription factors called STATs (signal transducers and activators of transcription), which enter the nucleus to promote gene transcription.

(Choice C) cAMP is cleaved by the enzyme cAMP phosphodiesterase to its inactive form, 5'-AMP. Drugs that inhibit cAMP phosphodiesterase lead to prolongation of the actions of cAMP. An example is the use of theophylline in bronchial asthma.

(Choice E) Ligands such as insulin and epidermal growth factor act through transmembrane receptors that have intrinsic tyrosine kinase domains.

Educational objective:
Protein kinase A is responsible for the intracellular effects of the G protein-mediated adenylate cyclase second messenger system. Hormone receptors that use this system include the TSH, glucagon, and PTH receptors.

References

- Glucagon receptors.

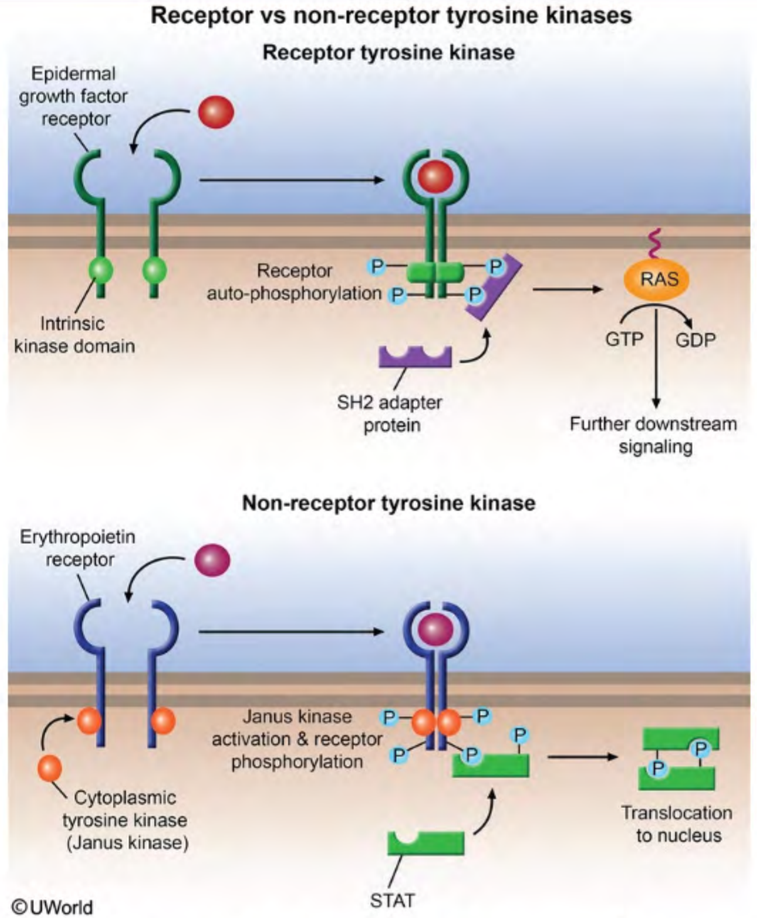
https://t.me/USMLEWorldStep1

binds GTP. **GTP binding** allows the alpha subunit to dissociate from the remainder of the G protein complex.

There
known
releas
A. Pr
activat
genes
(Choi
relaxa
cleave
specifi
(Choi
couple
cytoki
called
transc
(Choi
inhibit
in bron
(Choi
intrinsi
Educa
Protei
messe
Refere

- Glucagon receptors.

Exhibit Display



Zoom In Zoom Out Reset New | Existing My Notebook

https://t.me/USMLEWorldStep1

A couple comes to the clinic for preconception counseling. They are offered genetic screening because they are of Ashkenazi Jewish descent. Test results show that both are carriers for a lysosomal enzyme deficiency disorder that results in decreased metabolic degradation of a phospholipid substrate to ceramide, which leads to a buildup of the phospholipid. They are counseled about the chance that their offspring will be affected by this disorder. The couple wants to know the clinical features of an affected child. Which of the following findings would be most consistent with this condition?

- A. Abnormally shaped bones and corneal clouding
- B. Coarse facial features and cardiac dysfunction
- C. Neuropathic pain and angiokeratomas
- D. Retinal opacification and splenomegaly
- E. Small stature and infertility

Submit

https://t.me/USMLEWorldStep1

A couple comes to the clinic for preconception counseling. They are offered genetic screening because they are of Ashkenazi Jewish descent. Test results show that both are carriers for a lysosomal enzyme deficiency disorder that results in decreased metabolic degradation of a phospholipid substrate to ceramide, which leads to a buildup of the phospholipid. They are counseled about the chance that their offspring will be affected by this disorder. The couple wants to know the clinical features of an affected child. Which of the following findings would be most consistent with this condition?

- A. Abnormally shaped bones and corneal clouding (10%)
- ✗ B. Coarse facial features and cardiac dysfunction (12%)
- C. Neuropathic pain and angiokeratomas (31%)
- ✓ D. Retinal opacification and splenomegaly (42%)
- E. Small stature and infertility (2%)

Incorrect
Correct answer
D

42%
Answered correctly

04 secs
Time Spent

2023
Version

Explanation

Sphingolipidoses*

Diagnosis	Inheritance	Deficiency	Accumulated substrate	Key features
Fabry disease	XLR	α-Galactosidase A	Globotriaosylceramide	• Angiokeratomas • Peripheral neuropathy • Glomerulopathy
				• Macular cherry-red

https://t.me/USMLEWorldStep1

Sphingolipidoses*				
Diagnosis	**Inheritance**	**Deficiency**	**Accumulated substrate**	**Key features**
Fabry disease	XLR	α-Galactosidase A	Globotriaosylceramide	• Angiokeratomas • Peripheral neuropathy • Glomerulopathy
Tay-Sachs disease	AR	β-Hexosaminidase A	G_{M2} (ganglioside)	• Macular cherry-red spot • Progressive neurodegeneration
Gaucher disease		β-Glucocerebrosidase	Glucocerebroside	• Hepatosplenomegaly • Pancytopenia • Bone pain/osteopenia
Niemann-Pick disease		Sphingomyelinase	Sphingomyelin	• Macular cherry-red spot • Progressive neurodegeneration • Hepatosplenomegaly
Krabbe disease		Galactocerebrosidase	Galactocerebroside & psychosine	• Progressive neurodegeneration • Peripheral neuropathy • Optic atrophy
Metachromatic leukodystrophy		Arylsulfatase A	Cerebroside sulfate	• Progressive neurodegeneration • Peripheral neuropathy

https://t.me/USMLEWorldStep1

			substrate	
Fabry disease	XLR	α-Galactosidase A	Globotriaosylceramide	• Angiokeratomas • Peripheral neuropathy • Glomerulopathy
Tay-Sachs disease	AR	β-Hexosaminidase A	G_{M2} (ganglioside)	• Macular cherry-red spot • Progressive neurodegeneration
Gaucher disease		β-Glucocerebrosidase	Glucocerebroside	• Hepatosplenomegaly • Pancytopenia • Bone pain/osteopenia
Niemann-Pick disease		Sphingomyelinase	Sphingomyelin	• Macular cherry-red spot • Progressive neurodegeneration • Hepatosplenomegaly
Krabbe disease		Galactocerebrosidase	Galactocerebroside & psychosine	• Progressive neurodegeneration • Peripheral neuropathy • Optic atrophy
Metachromatic leukodystrophy		Arylsulfatase A	Cerebroside sulfate	• Progressive neurodegeneration • Peripheral neuropathy

* Subtype of lysosomal storage disorder.
AR = autosomal recessive; **XLR** = X-linked recessive.

Niemann-Pick disease is an autosomal recessive lysosomal storage disorder. It is caused by a **deficiency** of

https://t.me/USMLEWorldStep1

Niemann-Pick disease is an autosomal recessive lysosomal storage disorder. It is caused by a **deficiency** of **sphingomyelinase**, the enzyme responsible for metabolizing sphingomyelin (a phospholipid) to ceramide.

Excess sphingomyelin results in cells that appear enlarged, foamy, and vacuolated on electron microscopy. These lipid-laden foam cells accumulate in the liver (**hepatomegaly**), spleen (**splenomegaly**), and CNS (**hypotonia, neurodegeneration**). After a period of normal development, affected infants do not attain new skills and regress from previously acquired milestones (eg, sitting with support, head control, social smile). Accumulation of sphingomyelin in the retinal ganglion cells also leads to **retinal opacification**, which gives the appearance of a cherry-red macula. Disease is progressive, and death usually occurs by age 3.

Niemann-Pick disease, like several other rare genetic disorders (eg, Tay-Sachs disease, Gaucher disease, Bloom syndrome), is more common in the **Ashkenazi Jewish** population than in the general population. The increased risk for rare and often life-threatening genetic mutations is attributed to the founder effect, or the loss of genetic variability within a group that historically conceived within their own community. An Ashkenazi Jewish couple should be offered **genetic counseling** and testing before they conceive a child.

(Choices A and B) Hurler and Hunter syndromes are mucopolysaccharidoses characterized by the accumulation of heparan and dermatan sulfate, which are glycosaminoglycans (ie, polysaccharides, not phospholipids). Both disorders can cause dysostosis multiplex (eg, abnormally shaped bones, enlarged skull), coarse facial features, and cardiac dysfunction. Corneal clouding is unique to Hurler syndrome.

(Choice C) Fabry disease is characterized by decreased metabolic degradation of globotriaosylceramide to glucocerebroside, not ceramide. Disease manifestations include neuropathic pain and angiokeratomas in adolescence and multiorgan (eg, renal, cerebrovascular, cardiac) involvement in adulthood.

(Choice E) Small stature and infertility with a predisposition to malignancy and a classic sun-sensitive facial rash are typical signs of Bloom syndrome, an autosomal recessive disorder that leads to chromosomal instability, not phospholipid accumulation.

Educational objective:
Niemann-Pick disease is an autosomal recessive disorder that has a much higher incidence in the Ashkenazi Jewish population than in the general population. It is characterized by sphingomyelinase deficiency and

https://t.me/USMLEWorldStep1

Excess sphingomyelin results in cells that appear enlarged, foamy, and vacuolated on electron microscopy. These lipid-laden foam cells accumulate in the liver (**hepatomegaly**), spleen (**splenomegaly**), and CNS (**hypotonia, neurodegeneration**). After a period of normal development, affected infants do not attain new skills and regress from previously acquired milestones (eg, sitting with support, head control, social smile). Accumulation of sphingomyelin in the retinal ganglion cells also leads to **retinal opacification**, which gives the appearance of a cherry-red macula. Disease is progressive, and death usually occurs by age 3.

Niemann-Pick disease, like several other rare genetic disorders (eg, Tay-Sachs disease, Gaucher disease, Bloom syndrome), is more common in the **Ashkenazi Jewish** population than in the general population. The increased risk for rare and often life-threatening genetic mutations is attributed to the founder effect, or the loss of genetic variability within a group that historically conceived within their own community. An Ashkenazi Jewish couple should be offered **genetic counseling** and testing before they conceive a child.

(Choices A and B) Hurler and Hunter syndromes are mucopolysaccharidoses characterized by the accumulation of heparan and dermatan sulfate, which are glycosaminoglycans (ie, polysaccharides, not phospholipids). Both disorders can cause dysostosis multiplex (eg, abnormally shaped bones, enlarged skull), coarse facial features, and cardiac dysfunction. Corneal clouding is unique to Hurler syndrome.

(Choice C) Fabry disease is characterized by decreased metabolic degradation of globotriaosylceramide to glucocerebroside, not ceramide. Disease manifestations include neuropathic pain and angiokeratomas in adolescence and multiorgan (eg, renal, cerebrovascular, cardiac) involvement in adulthood.

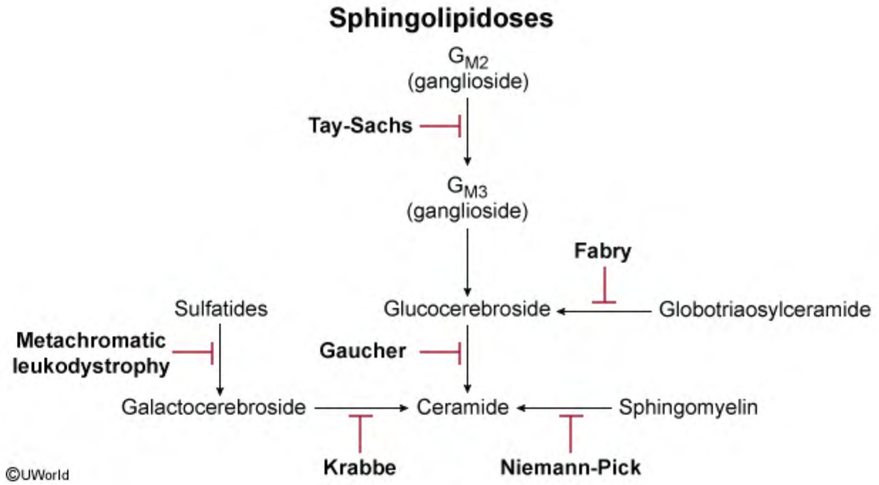
(Choice E) Small stature and infertility with a predisposition to malignancy and a classic sun-sensitive facial rash are typical signs of Bloom syndrome, an autosomal recessive disorder that leads to chromosomal instability, not phospholipid accumulation.

Educational objective:
Niemann-Pick disease is an autosomal recessive disorder that has a much higher incidence in the Ashkenazi Jewish population than in the general population. It is characterized by sphingomyelinase deficiency and sphingomyelin (phospholipid) accumulation, which cause neurologic regression, hepatosplenomegaly, and retinal opacification (ie, cherry-red macula).

https://t.me/USMLEWorldStep1

leukodystrophy			• Peripheral neuropathy

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Niema
sphin

Exces
lipid-la
neuro
from p
sphing
cherry

Niema
syndro
risk fo
variab
should

(Choi
of hep
disord
and ca

(Choi
glucoc
adoles

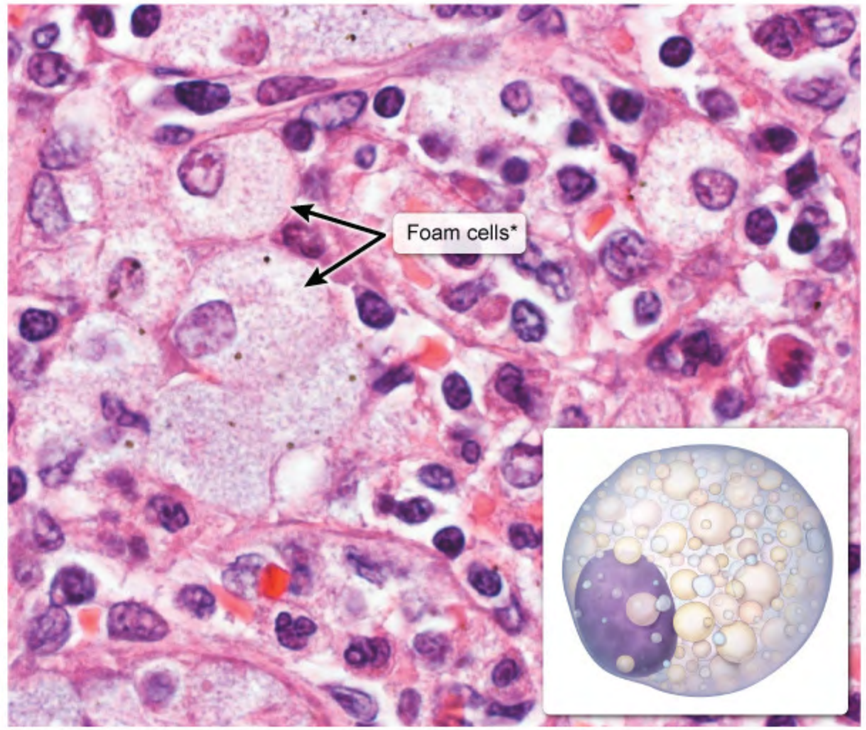
(Choi
are typical signs of Bloom syndrome, an autosomal recessive disorder that leads to chromosomal instability, not phospholipid accumulation.

https://t.me/USMLEWorldStep1

leukodystrophy				• Peripheral neuropathy

Exhibit Display

Niemann-Pick disease



*Macrophages with foamy cytoplasm due to sphingomyelin accumulation in lysosomes. ©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Niema
sphin

Exces
lipid-la
neuro
from p
sphing
cherry

Niema
syndro
risk fo
variab
should

(Choi
of hep
disord
and ca

(Choi
glucoc
adoles

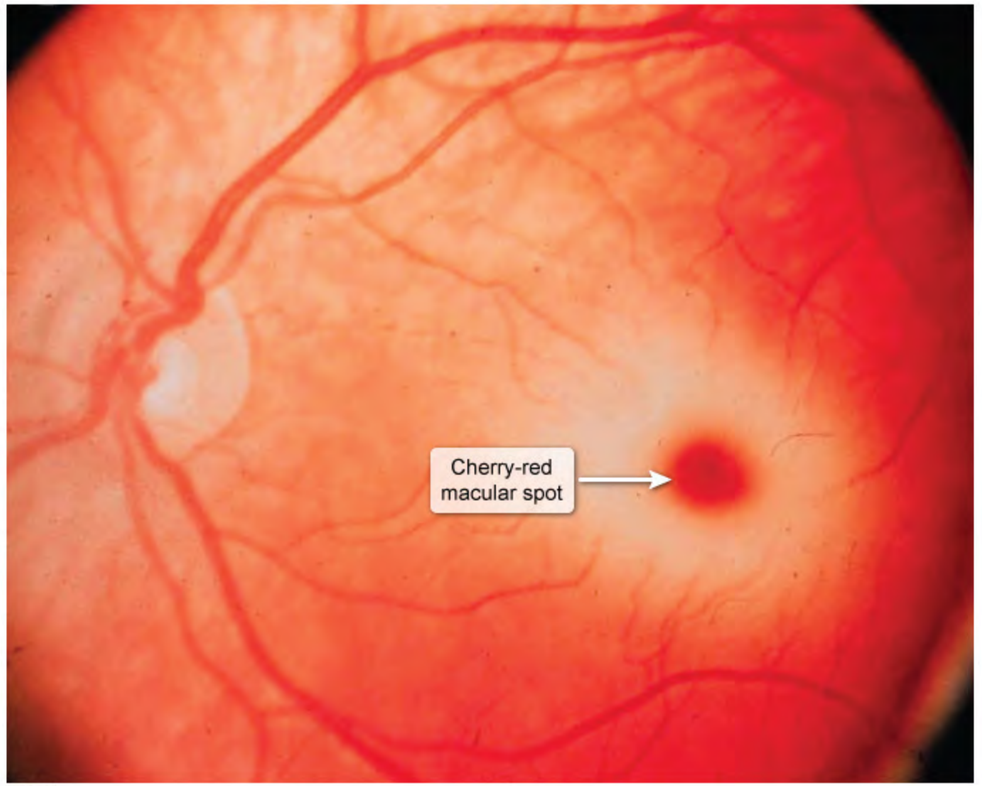
(Choi
are typical signs of Bloom syndrome, an autosomal recessive disorder that leads to chromosomal instability, not phospholipid accumulation.

https://t.me/USMLEWorldStep1

leukodystrophy				• Peripheral neuropathy

Exhibit Display

Cherry-red macular spot



©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Niema
sphin

Exces
lipid-la
neuro
from p
sphing
cherry

Niema
syndro
risk fo
variab
should

(Choi
of hep
disord
and ca

(Choi
glucoc
adoles

(Choi
are typical signs of Bloom syndrome, an autosomal recessive disorder that leads to chromosomal instability, not phospholipid accumulation.

https://t.me/USMLEWorldStep1

A 16-year-old boy is brought to the office for evaluation of irritability, slow growth, and acne. The patient plays soccer and has been following an aggressive strength-training program. When asked, he admits to using a performance-enhancing substance for the past 6 months. What additional findings would most likely be present in this patient now compared to 6 months ago?

	Serum LH	Serum estrogen	Spermatogenesis
○ A.	High	High	High
○ B.	High	High	Low
○ C.	High	Low	Low
○ D.	Low	High	High
○ E.	Low	High	Low
○ F.	Low	Low	Low

Submit

https://t.me/USMLEWorldStep1

A 16-year-old boy is brought to the office for evaluation of irritability, slow growth, and acne. The patient plays soccer and has been following an aggressive strength-training program. When asked, he admits to using a performance-enhancing substance for the past 6 months. What additional findings would most likely be present in this patient now compared to 6 months ago?

		Serum LH	Serum estrogen	Spermatogenesis	
	A.	High	High	High	(1%)
✗	B.	High	High	Low	(8%)
	C.	High	Low	Low	(4%)
	D.	Low	High	High	(4%)
✓	E.	Low	High	Low	(62%)
	F.	Low	Low	Low	(17%)

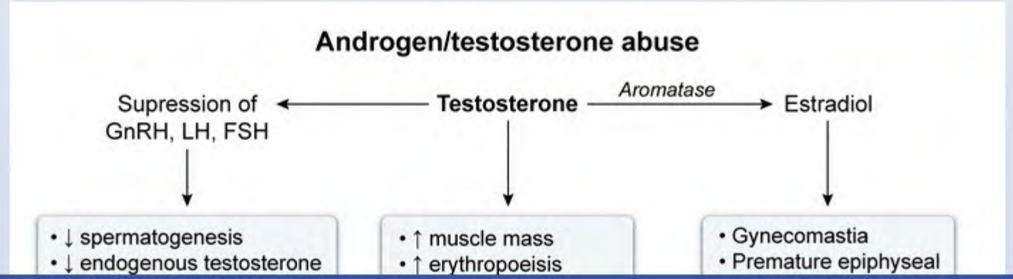
Incorrect
Correct answer
E

62%
Answered correctly

18 secs
Time Spent

2023
Version

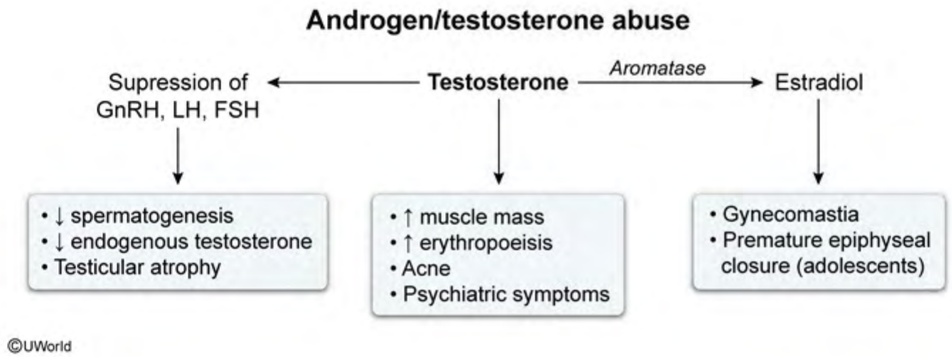
Explanation



https://t.me/USMLEWorldStep1

A 16-year-old boy is brought to the office for evaluation of irritability, slow growth, and acne. The patient plays
socce
perfor
this pa

Exhibit Display



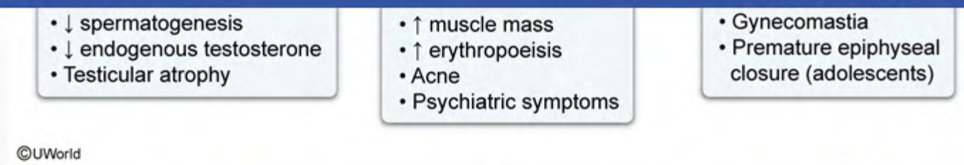
Zoom In Zoom Out Reset New | Existing My Notebook

Inco
Corre
E

Expl

• ↓ spermatogenesis
• ↓ endogenous testosterone
• ↑ muscle mass
• ↑ erythropoeisis
• Gynecomastia
• Premature epiphyseal

https://t.me/USMLEWorldStep1



Testosterone stimulates increased protein synthesis by skeletal myocytes. Some competitive athletes and body builders **abuse testosterone** and other exogenous androgens to increase muscle mass and improve athletic performance. However, excessive androgenic activity can cause significant adverse effects, including **acne** (increased dermal sebum production) and neuropsychiatric changes (eg, **irritability, aggression**, and anxiety).

Androgen abuse can also result in profound endocrine and reproductive effects. Spermatogenesis in the seminiferous tubules is driven by FSH and requires a high local concentration of testosterone, which is produced by nearby Leydig cells and retained by androgen-binding protein. Exogenous androgens suppress GnRH, LH, and FSH secretion, leading to reduced endogenous testosterone secretion, **impaired spermatogenesis (Choice D)**, and **testicular atrophy**.

In addition, excess testosterone is converted by aromatase to yield high levels of estradiol **(Choice F)**, which can lead to **gynecomastia**. In adolescent users, high circulating estrogen levels can also cause **premature epiphyseal closure** and short stature.

(Choices A, B, and C) Excess circulating exogenous androgens (eg, testosterone) suppress pituitary LH release.

Educational objective:
Androgen abuse suppresses GnRH, LH, and FSH secretion, leading to reduced endogenous testosterone secretion, impaired spermatogenesis, and testicular atrophy. In addition, excess testosterone is converted by aromatase to estradiol, which can lead to gynecomastia.

References

- Performance-enhancing drug use in adolescence.

Physiology	Endocrine, Diabetes & Metabolism	Infertility
Subject	System	Topic

Copyright © UWorld. All rights reserved.

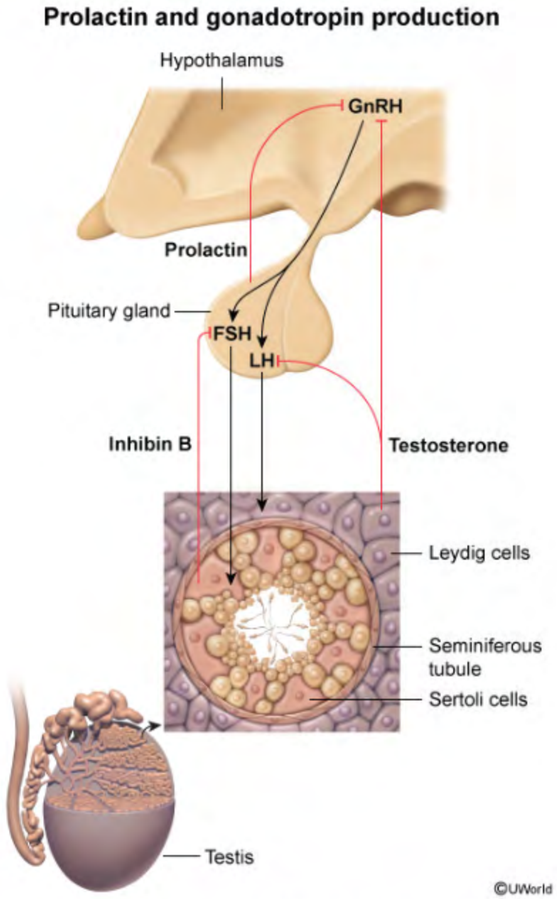
https://t.me/USMLEWorldStep1

- ↓ spermatogenesis
- ↓ endogenous testosterone

- ↑ muscle mass
- ↑ erythropoeisis

- Gynecomastia
- Premature epiphyseal

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Testos
builde
perfor
(increa

Andro
semini
by nea
FSH s
and **te**

In add
lead to
epiphy

(Choi

Educa
Andro
secret
aroma

Refere
- Per

Physiolo
Subject

Copyright © UWorld. All rights reserved.

https://t.me/USMLEWorldStep1

A 29-year-old nulligravid woman comes to the office due to a 2-month history of worsening bilateral nipple discharge that stains her bra. The patient has felt no breast mass and has had no breast pain, headaches, or vision changes. Her last menstrual period was 3 months ago, and home pregnancy tests have been negative. Previously, she had regular menstrual cycles at 28-day intervals. The patient has no other medical conditions and takes no medications. Vital signs are within normal limits. On physical examination, visual fields are intact by confrontation. A whitish fluid can be expressed bilaterally on nipple compression. There are no breast masses or lymphadenopathy. Pelvic examination reveals no abnormalities. Serum beta-hCG testing is negative. Brain imaging shows a 0.6-cm pituitary mass. Pharmacotherapeutic treatment is begun, and on a follow-up visit the patient reports that her symptoms are improving. Which of the following is the most likely mechanism of action of this medication?

- A. Increased estrogen effect on the pituitary
- B. Inhibition of gonadotropin-releasing hormone secretion
- C. Inhibition of hypothalamic dopaminergic neurons
- D. Stimulation of pituitary dopamine receptors
- E. Stimulation of thyrotropin-releasing hormone receptors

Submit

https://t.me/USMLEWorldStep1

A 29-year-old nulligravid woman comes to the office due to a 2-month history of worsening bilateral nipple discharge that stains her bra. The patient has felt no breast mass and has had no breast pain, headaches, or vision changes. Her last menstrual period was 3 months ago, and home pregnancy tests have been negative. Previously, she had regular menstrual cycles at 28-day intervals. The patient has no other medical conditions and takes no medications. Vital signs are within normal limits. On physical examination, visual fields are intact by confrontation. A whitish fluid can be expressed bilaterally on nipple compression. There are no breast masses or lymphadenopathy. Pelvic examination reveals no abnormalities. Serum beta-hCG testing is negative. Brain imaging shows a 0.6-cm pituitary mass. Pharmacotherapeutic treatment is begun, and on a follow-up visit the patient reports that her symptoms are improving. Which of the following is the most likely mechanism of action of this medication?

- ✗ A. Increased estrogen effect on the pituitary (1%)
- B. Inhibition of gonadotropin-releasing hormone secretion (4%)
- C. Inhibition of hypothalamic dopaminergic neurons (8%)
- ✓ D. Stimulation of pituitary dopamine receptors (84%)
- E. Stimulation of thyrotropin-releasing hormone receptors (1%)

Incorrect
Correct answer
D

84%
Answered correctly

04 secs
Time Spent

2023
Version

Explanation

Prolactinoma	
Clinical features	• **Premenopausal women**: oligomenorrhea/amenorrhea, infertility, galactorrhea, hot flashes, decreased bone density • **Postmenopausal women**: mass-effect symptoms (headache, visual field defects)

https://t.me/USMLEWorldStep1

Prolactinoma	
Clinical features	• **Premenopausal women**: oligomenorrhea/amenorrhea, infertility, galactorrhea, hot flashes, decreased bone density • **Postmenopausal women**: mass-effect symptoms (headache, visual field defects) • **Men**: infertility, decreased libido, impotence, gynecomastia
Laboratory/ imaging	• Serum prolactin (often >200 ng/mL) • Tests to rule out renal insufficiency (creatinine) & hypothyroidism (TSH, thyroxine) • MRI of the head/pituitary
Treatment	• Dopamine agonist (cabergoline) • Transsphenoidal surgery

Galactorrhea is abnormal secretion of breast milk not associated with pregnancy or breastfeeding. It is most commonly due to excess prolactin, which directly stimulates milk secretion in the breasts. Pituitary lactotroph adenomas (**prolactinomas**) can cause very high prolactin levels and are a common cause of galactorrhea.

Unlike most pituitary hormones, which are under positive regulation by releasing hormones from the hypothalamus, prolactin is primarily under negative regulation by hypothalamic dopaminergic neurons via the pituitary stalk. Because of the tonic inhibitory effect of dopamine on prolactin secretion, **dopamine agonists** (eg, cabergoline, bromocriptine) can be used to treat hyperprolactinemia. Dopamine agonist therapy reduces adenoma size, suppresses prolactin production, and, in patients with small (<1 cm, as in this patient) prolactinomas and no mass-effect symptoms (eg, headache, visual field defects), can often induce a prolonged clinical response.

(Choices A and C) Estrogen stimulates prolactin gene transcription and secretion. Strongly estrogenic medications (eg, birth control pills) can potentially worsen rather than alleviate galactorrhea. Dopamine antagonists (eg, antipsychotics) directly increase prolactin secretion and also can worsen galactorrhea.

(Choice B) Hyperprolactinemia causes amenorrhea in women due to the inhibitory effect of prolactin on hypothalamic GnRH release. Dopaminergic medications suppress prolactin secretion and can restore normal GnRH secretion.

https://t.me/USMLEWorldStep1

Treatment	• Dopamine agonist (cabergoline) • Transsphenoidal surgery

Galactorrhea is abnormal secretion of breast milk not associated with pregnancy or breastfeeding. It is most commonly due to excess prolactin, which directly stimulates milk secretion in the breasts. Pituitary lactotroph adenomas (**prolactinomas**) can cause very high prolactin levels and are a common cause of galactorrhea.

Unlike most pituitary hormones, which are under positive regulation by releasing hormones from the hypothalamus, prolactin is primarily under negative regulation by hypothalamic dopaminergic neurons via the pituitary stalk. Because of the tonic inhibitory effect of dopamine on prolactin secretion, **dopamine agonists** (eg, cabergoline, bromocriptine) can be used to treat hyperprolactinemia. Dopamine agonist therapy reduces adenoma size, suppresses prolactin production, and, in patients with small (<1 cm, as in this patient) prolactinomas and no mass-effect symptoms (eg, headache, visual field defects), can often induce a prolonged clinical response.

(Choices A and C) Estrogen stimulates prolactin gene transcription and secretion. Strongly estrogenic medications (eg, birth control pills) can potentially worsen rather than alleviate galactorrhea. Dopamine antagonists (eg, antipsychotics) directly increase prolactin secretion and also can worsen galactorrhea.

(Choice B) Hyperprolactinemia causes amenorrhea in women due to the inhibitory effect of prolactin on hypothalamic GnRH release. Dopaminergic medications suppress prolactin secretion and can restore normal GnRH secretion.

(Choice E) Thyrotropin-releasing hormone (TRH) stimulates secretion of prolactin by lactotrophs, although its role in regulating prolactin release is secondary to the inhibition of prolactin secretion by dopamine. Factors that increase TRH release would worsen hyperprolactinemia.

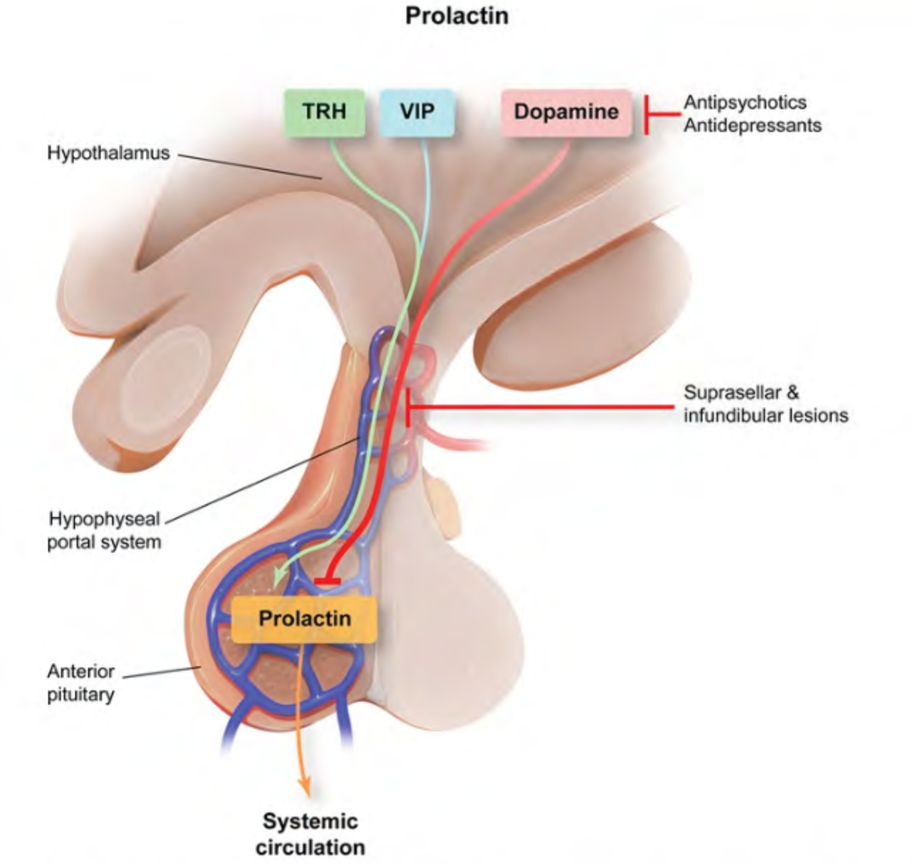
Educational objective:
Galactorrhea is abnormal secretion of breast milk not associated with pregnancy or breastfeeding. It is most commonly due to excess prolactin, as seen in prolactin-secreting pituitary adenomas. Prolactin is under negative regulation by hypothalamic dopaminergic neurons, and dopamine agonists can be used to treat hyperprolactinemia.

References

https://t.me/USMLEWorldStep1

Laboratory/	• Serum prolactin (often >200 ng/mL)

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Galac
comm
adeno

Unlike
prolac
Becau
bromo
suppre
effect

(Choi
medic
antago

(Choi
hypoth
GnRH

(Choi
in regu
increa

Educa
Galactorrhea is abnormal secretion of breast milk not associated with pregnancy or breastfeeding. It is most commonly due to excess prolactin, as seen in prolactin-secreting pituitary adenomas. Prolactin is under negative

https://t.me/USMLEWorldStep1

A 54-year-old woman is evaluated for a painless thyroid nodule. She has had no weight changes, heat or cold intolerance, hoarseness, or dyspnea. Medical history is notable for mild hypertension, for which she takes appropriate medications. The patient does not use tobacco or alcohol. Physical examination shows a 3-cm, firm nodule in the right thyroid lobe and enlarged, right cervical lymph nodes. TSH is normal, and fine-needle aspiration of the nodule shows papillary structures with nuclear atypia. Total thyroidectomy is planned. During the surgery, a nearby nerve is injured while ligating an artery entering the superior pole of the thyroid lobe. Which of the following muscles is most likely to be denervated as a result of this injury?

- A. Aryepiglotticus
- B. Cricothyroid
- C. Lateral cricoarytenoid
- D. Posterior cricoarytenoid
- E. Thyroarytenoid

Submit

https://t.me/USMLEWorldStep1

A 54-year-old woman is evaluated for a painless thyroid nodule. She has had no weight changes, heat or cold intolerance, hoarseness, or dyspnea. Medical history is notable for mild hypertension, for which she takes appropriate medications. The patient does not use tobacco or alcohol. Physical examination shows a 3-cm, firm nodule in the right thyroid lobe and enlarged, right cervical lymph nodes. TSH is normal, and fine-needle aspiration of the nodule shows papillary structures with nuclear atypia. Total thyroidectomy is planned. During the surgery, a nearby nerve is injured while ligating an artery entering the superior pole of the thyroid lobe. Which of the following muscles is most likely to be denervated as a result of this injury?

- A. Aryepiglotticus (3%)
- ✓ B. Cricothyroid (69%)
- C. Lateral cricoarytenoid (12%)
- D. Posterior cricoarytenoid (7%)
- E. Thyroarytenoid (6%)

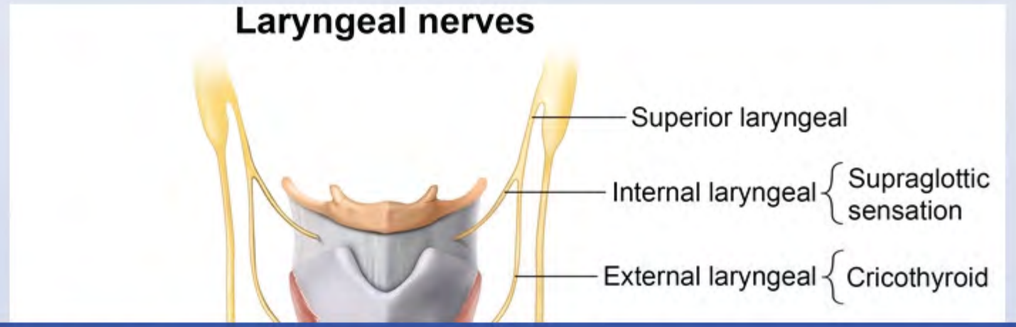
Correct

69%
Answered correctly

03 secs
Time Spent

2023
Version

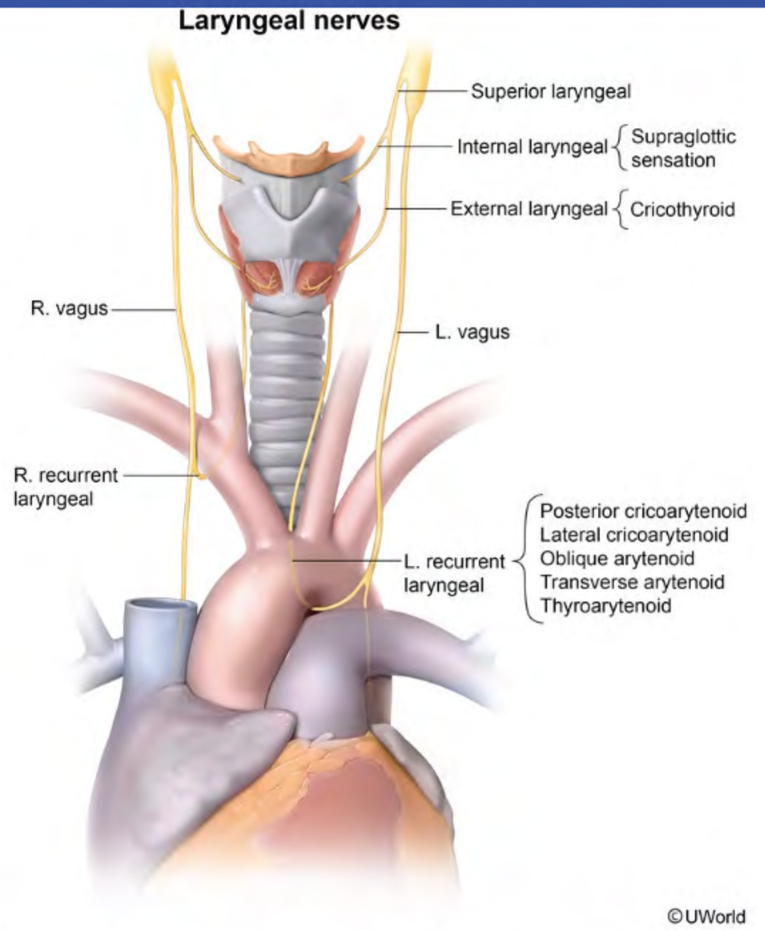
Explanation



https://t.me/USMLEWorldStep1

A 54-year-old woman is evaluated for a painless thyroid nodule. She has had no weight changes, heat or cold intoler
approp
nodule
of the
nearby
muscle

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

External laryngeal { Cricothyroid

https://t.me/USMLEWorldStep1



©UWorld

The superior thyroid artery (a branch of the external carotid artery) and the inferior thyroid artery (a branch of the thyrocervical trunk) provide the blood supply to the thyroid and parathyroid glands. The **superior thyroid artery** and vein and **external branch of the superior laryngeal nerve** course together in a neurovascular triad that originates superior to the thyroid gland and lateral to the thyroid cartilage. The external branch is at risk of injury during thyroidectomy as it courses just deep to the superior thyroid artery.

The **cricothyroid muscle** is the only muscle innervated by this nerve. It originates on the cricoid cartilage and inserts on the lower border of the thyroid cartilage. The cricothyroid muscle acts to tense the vocal cords, and denervation injury may cause a low, hoarse voice with limited range of pitch. The internal branch of the superior laryngeal nerve does not innervate any muscles but provides sensory innervation to the laryngeal mucosa above the vocal folds.

(Choices A, C, D, and E) The remaining laryngeal muscles are innervated by the recurrent laryngeal nerves, which also provide sensory innervation to the larynx below the vocal folds. The recurrent laryngeal nerves lie posterior to the thyroid, near the inferior thyroid arteries. These nerves can be injured during thyroidectomy but do not run with the superior thyroid artery at the superior pole of the thyroid.

Educational objective:
The external branch of the superior laryngeal nerve is at risk of injury during thyroidectomy due to its proximity to the superior thyroid artery and vein. This nerve innervates the cricothyroid muscle.

References

- Identification of the external branch of the superior laryngeal nerve during thyroidectomy.

Anatomy	Endocrine, Diabetes & Metabolism	Thyroid cancer
Subject	System	Topic

Copyright © UWorld. All rights reserved.

https://t.me/USMLEWorldStep1

A 19-year-old woman comes to the office for evaluation of amenorrhea. The patient underwent menarche at age 12, and she previously had menses regularly every 25-28 days. However, for the past year, her menses have been irregular, and her last menstrual period was 3 months ago. The patient has no significant medical history, eats mainly fruits and vegetables, and exercises regularly at a local gym. On further questioning, she expresses concern about being overweight and asks for suggestions on cutting down her caloric intake. BMI is 18 kg/m^2. The patient is thin and has dry skin covered by fine, downy hair. A pregnancy test is negative. Which of the following laboratory findings are most likely present in this patient?

	GnRH	FSH	Estradiol
○ A.	Increased	Increased	Decreased
○ B.	Increased	Decreased	Decreased
○ C.	Decreased	Normal	Normal
○ D.	Decreased	Decreased	Decreased
○ E.	Normal	Normal	Decreased

Submit

https://t.me/USMLEWorldStep1

A 19-year-old woman comes to the office for evaluation of amenorrhea. The patient underwent menarche at age 12, and she previously had menses regularly every 25-28 days. However, for the past year, her menses have been irregular, and her last menstrual period was 3 months ago. The patient has no significant medical history, eats mainly fruits and vegetables, and exercises regularly at a local gym. On further questioning, she expresses concern about being overweight and asks for suggestions on cutting down her caloric intake. BMI is 18 kg/m^2. The patient is thin and has dry skin covered by fine, downy hair. A pregnancy test is negative. Which of the following laboratory findings are most likely present in this patient?

		GnRH	FSH	Estradiol	
	A.	Increased	Increased	Decreased	(9%)
✗	B.	Increased	Decreased	Decreased	(10%)
	C.	Decreased	Normal	Normal	(1%)
✓	D.	Decreased	Decreased	Decreased	(76%)
	E.	Normal	Normal	Decreased	(2%)

Incorrect
Correct answer
D

76%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

Functional hypothalamic amenorrhea

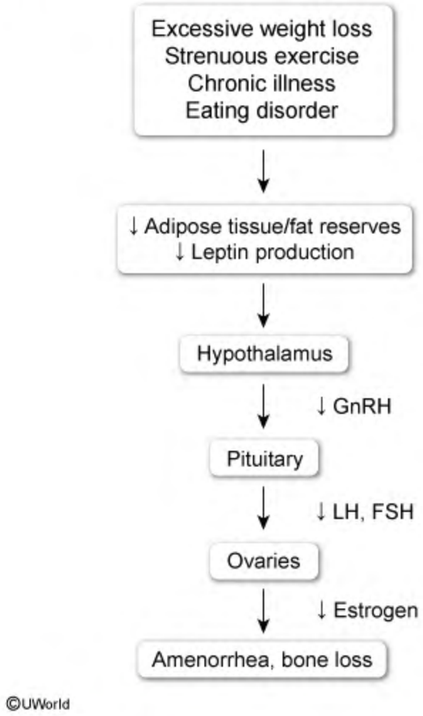
Excessive weight loss
Strenuous exercise
Chronic illness
Eating disorder

https://t.me/USMLEWorldStep1

A 19-year-old woman comes to the office for evaluation of amenorrhea. The patient underwent menarche at age 12, an
been i
eats m
concer
The pa
followi

Exhibit Display

Functional hypothalamic amenorrhea



©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Eating disorder

https://t.me/USMLEWorldStep1

Amenorrhea is categorized as primary (no onset of menarche by age 15) or secondary (no menses for ≥3 months in premenopausal patients with previously regular menses). This patient has **secondary amenorrhea**, which usually occurs due to endocrine dysfunction (eg, hypothalamic-pituitary-ovarian axis dysfunction, thyroid disorder), pregnancy, or intrauterine adhesions (ie, Asherman syndrome).

This patient's distorted body image (feeling overweight despite underweight BMI), restricted diet, exercise regimen, dry skin, and lanugo (fine hair indicating inadequate caloric intake) suggest **anorexia nervosa**, a common cause of **functional hypothalamic amenorrhea** (FHA). The pathophysiology of FHA is incompletely understood but is thought to arise due to diminished adipose tissue stores, which reduce circulating leptin levels. In response, the hypothalamus decreases the amplitude and frequency of pulsatile gonadotropin-releasing hormone (GnRH) release, leading to **low GnRH** levels, **decreased pituitary LH and FSH** secretion, **low circulating estrogen** levels, anovulation, and amenorrhea **(Choices C and E)**.

In addition to anorexia nervosa, FHA can also occur when caloric expenditure is out of proportion to intake, such as in female **athletes** (eg, distance runners, dancers) or patients with chronic illness, particularly those with low adipose stores. FHA is a form of hypogonadotrophic (low LH and FSH) hypogonadism (low estrogen). Therefore, potential complications in young patients include reduced peak bone mass, which may lead to early-onset **osteoporosis**.

(Choice A) Low circulating estrogen levels despite increased GnRH and FSH secretion are consistent with a primary ovarian disorder (eg, primary ovarian insufficiency [POI], menopause). POI is associated with Turner syndrome and prior chemoradiation, not anorexia nervosa.

(Choice B) Pituitary dysfunction, which includes anatomic (eg, prolactinoma) and functional disorders (eg, hypopituitarism due to infarction [Sheehan syndrome]), can cause hypogonadotropic hypogonadism and amenorrhea characterized by increased GnRH, low FSH and LH, and low estrogen. However, prolactinomas typically present with additional clinical features (eg, bilateral galactorrhea), and Sheehan syndrome is usually associated with prior hemorrhage, particularly obstetric hemorrhage.

Educational objective:
Functional hypothalamic amenorrhea is a common cause of secondary amenorrhea and occurs due to decreased amplitude and frequency of pulsatile gonadotropin-releasing hormone release from the hypothalamus, which in

https://t.me/USMLEWorldStep1

pregnancy, or intrauterine adhesions (ie, Asherman syndrome).

This patient's distorted body image (feeling overweight despite underweight BMI), restricted diet, exercise regimen, dry skin, and lanugo (fine hair indicating inadequate caloric intake) suggest **anorexia nervosa**, a common cause of **functional hypothalamic amenorrhea** (FHA). The pathophysiology of FHA is incompletely understood but is thought to arise due to diminished adipose tissue stores, which reduce circulating leptin levels. In response, the hypothalamus decreases the amplitude and frequency of pulsatile gonadotropin-releasing hormone (GnRH) release, leading to **low GnRH** levels, **decreased pituitary LH and FSH** secretion, **low circulating estrogen** levels, anovulation, and amenorrhea **(Choices C and E)**.

In addition to anorexia nervosa, FHA can also occur when caloric expenditure is out of proportion to intake, such as in female **athletes** (eg, distance runners, dancers) or patients with chronic illness, particularly those with low adipose stores. FHA is a form of hypogonadotrophic (low LH and FSH) hypogonadism (low estrogen). Therefore, potential complications in young patients include reduced peak bone mass, which may lead to early-onset **osteoporosis**.

(Choice A) Low circulating estrogen levels despite increased GnRH and FSH secretion are consistent with a primary ovarian disorder (eg, primary ovarian insufficiency [POI], menopause). POI is associated with Turner syndrome and prior chemoradiation, not anorexia nervosa.

(Choice B) Pituitary dysfunction, which includes anatomic (eg, prolactinoma) and functional disorders (eg, hypopituitarism due to infarction [Sheehan syndrome]), can cause hypogonadotropic hypogonadism and amenorrhea characterized by increased GnRH, low FSH and LH, and low estrogen. However, prolactinomas typically present with additional clinical features (eg, bilateral galactorrhea), and Sheehan syndrome is usually associated with prior hemorrhage, particularly obstetric hemorrhage.

Educational objective:
Functional hypothalamic amenorrhea is a common cause of secondary amenorrhea and occurs due to decreased amplitude and frequency of pulsatile gonadotropin-releasing hormone release from the hypothalamus, which in turn leads to low FSH, LH, and estrogen levels. Causes include anorexia nervosa (eg, distorted body image, restricted diet, lanugo), excessive strenuous exercise, and chronic illness.

References

https://t.me/USMLEWorldStep1

A 50-year-old man is brought to the emergency department due to a sudden, severe headache associated with nausea and vomiting that started earlier in the day. The patient has had mild headaches and decreased libido over the past 3 months. He has no other medical conditions and takes no medications. Physical examination reveals bilateral visual field deficits and impaired extraocular eye movements on the right side. Shortly after being admitted to the hospital, he becomes acutely hypotensive and loses consciousness. The patient dies despite aggressive resuscitation efforts. Which of the following is most likely to be found on autopsy?

- A. Acute hemorrhage in the pituitary gland
- B. Bleeding within the putamen
- C. Dissection of the internal carotid artery
- D. Ruptured intracranial aneurysm
- E. Thrombus in the cavernous venous sinuses

Submit

https://t.me/USMLEWorldStep1

A 50-year-old man is brought to the emergency department due to a sudden, severe headache associated with nausea and vomiting that started earlier in the day. The patient has had mild headaches and decreased libido over the past 3 months. He has no other medical conditions and takes no medications. Physical examination reveals bilateral visual field deficits and impaired extraocular eye movements on the right side. Shortly after being admitted to the hospital, he becomes acutely hypotensive and loses consciousness. The patient dies despite aggressive resuscitation efforts. Which of the following is most likely to be found on autopsy?

- ✓ A. Acute hemorrhage in the pituitary gland (68%)
- B. Bleeding within the putamen (0%)
- ✗ C. Dissection of the internal carotid artery (2%)
- D. Ruptured intracranial aneurysm (21%)
- E. Thrombus in the cavernous venous sinuses (7%)

Incorrect
Correct answer
A

68% Answered correctly
04 secs Time Spent
2023 Version

Explanation

Pituitary apoplexy	
Pathogenesis	• Acute pituitary hemorrhage • Usually occurs in preexisting adenoma
Clinical	• Severe headache • Bitemporal hemianopia (optic chiasm) &

https://t.me/USMLEWorldStep1

Pituitary apoplexy	
Pathogenesis	• Acute pituitary hemorrhage • Usually occurs in preexisting adenoma
Clinical presentation	• Severe headache • Bitemporal hemianopia (optic chiasm) & ophthalmoplegia (CN III) • Hemodynamic instability & altered sensorium
Complications	• Panhypopituitarism (acute & chronic) • Severe hypotension (central adrenal failure) • Coma & death

This patient had typical features of acute pituitary hemorrhage (**pituitary apoplexy**), including a severe **headache**, **bitemporal hemianopsia** (due to compression of the optic chiasm), and **ophthalmoplegia** (due to compression of the oculomotor nerve [CN III]). Pituitary apoplexy usually occurs in a preexisting **pituitary adenoma**, as in this patient with chronic headaches and low libido (likely due to hyperprolactinemia). The diagnosis can be confirmed on cross-sectional imaging (MRI scan).

Pituitary apoplexy typically causes loss of all pituitary function; **acute loss of ACTH** secretion can lead to **adrenal crisis** (acute central adrenal insufficiency). **Cortisol** helps maintain vascular tone by potentiating the vasoconstrictive effects of catecholamines (eg, norepinephrine); in the absence of ACTH, the adrenal cortex ceases production of cortisol, leading to **severe hypotension** and **distributive shock**. Pituitary apoplexy is a medical emergency that requires urgent treatment with **glucocorticoids** and neurosurgical consultation.

(Choice B) Hemorrhage into the putamen (basal ganglia) causes neurologic deficits that gradually worsen over minutes to hours. Typical features include contralateral hemiparesis and hemianesthesia due to disruption of the

https://t.me/USMLEWorldStep1

This patient had typical features of acute pituitary hemorrhage (**pituitary apoplexy**), including a severe **headache**, **bitemporal hemianopsia** (due to compression of the optic chiasm), and **ophthalmoplegia** (due to compression of the oculomotor nerve [CN III]). Pituitary apoplexy usually occurs in a preexisting **pituitary adenoma**, as in this patient with chronic headaches and low libido (likely due to hyperprolactinemia). The diagnosis can be confirmed on cross-sectional imaging (MRI scan).

Pituitary apoplexy typically causes loss of all pituitary function; **acute loss of ACTH** secretion can lead to **adrenal crisis** (acute central adrenal insufficiency). **Cortisol** helps maintain vascular tone by potentiating the vasoconstrictive effects of catecholamines (eg, norepinephrine); in the absence of ACTH, the adrenal cortex ceases production of cortisol, leading to **severe hypotension** and **distributive shock**. Pituitary apoplexy is a medical emergency that requires urgent treatment with **glucocorticoids** and neurosurgical consultation.

(Choice B) Hemorrhage into the putamen (basal ganglia) causes neurologic deficits that gradually worsen over minutes to hours. Typical features include contralateral hemiparesis and hemianesthesia due to disruption of the corticospinal and somatosensory tracts. It is most often seen in chronic hypertensive vasculopathy.

(Choice C) Carotid dissection typically presents with unilateral headache, transient vision loss, ptosis, and miosis (partial Horner syndrome). It usually occurs following trauma or can occur spontaneously in patients with chronic hypertension, connective tissue disease, or history of smoking.

(Choice D) Subarachnoid hemorrhage (SAH) due to rupture of a saccular aneurysm near the optic chiasm can present similarly to pituitary apoplexy. However, SAH is usually associated with hypertension due to sympathetic activation, and it is unusual for an aneurysm to cause both bilateral visual field defects (compression of the optic chiasm) and ophthalmoplegia (compression of the CN III or trochlear nerve [CN IV]). This patient's chronic history of decreased libido followed by acute cardiovascular collapse is more suggestive of a pituitary etiology.

(Choice E) Cavernous sinus thrombosis is most common in patients with underlying thrombophilia, pregnancy, oral contraceptive use, malignancy, or infection. Presenting features include progressively worse headaches, vomiting, seizures, and oculomotor deficits (similar to pituitary mass compression). However, chronically decreased libido, bitemporal hemianopsia, and sudden death from hypotension would be unusual.

Educational objective:

https://t.me/USMLEWorldStep1

crisis (acute central adrenal insufficiency). **Cortisol** helps maintain vascular tone by potentiating the vasoconstrictive effects of catecholamines (eg, norepinephrine); in the absence of ACTH, the adrenal cortex ceases production of cortisol, leading to **severe hypotension** and **distributive shock**. Pituitary apoplexy is a medical emergency that requires urgent treatment with **glucocorticoids** and neurosurgical consultation.

(Choice B) Hemorrhage into the putamen (basal ganglia) causes neurologic deficits that gradually worsen over minutes to hours. Typical features include contralateral hemiparesis and hemianesthesia due to disruption of the corticospinal and somatosensory tracts. It is most often seen in chronic hypertensive vasculopathy.

(Choice C) Carotid dissection typically presents with unilateral headache, transient vision loss, ptosis, and miosis (partial Horner syndrome). It usually occurs following trauma or can occur spontaneously in patients with chronic hypertension, connective tissue disease, or history of smoking.

(Choice D) Subarachnoid hemorrhage (SAH) due to rupture of a saccular aneurysm near the optic chiasm can present similarly to pituitary apoplexy. However, SAH is usually associated with hypertension due to sympathetic activation, and it is unusual for an aneurysm to cause both bilateral visual field defects (compression of the optic chiasm) and ophthalmoplegia (compression of the CN III or trochlear nerve [CN IV]). This patient's chronic history of decreased libido followed by acute cardiovascular collapse is more suggestive of a pituitary etiology.

(Choice E) Cavernous sinus thrombosis is most common in patients with underlying thrombophilia, pregnancy, oral contraceptive use, malignancy, or infection. Presenting features include progressively worse headaches, vomiting, seizures, and oculomotor deficits (similar to pituitary mass compression). However, chronically decreased libido, bitemporal hemianopsia, and sudden death from hypotension would be unusual.

Educational objective:
Acute pituitary hemorrhage (pituitary apoplexy) is characterized by severe headache, bitemporal hemianopsia (compression of the optic chiasm), and ophthalmoplegia (compression of the oculomotor nerve [CN III]). It usually occurs in a preexisting pituitary adenoma. Pituitary apoplexy is a medical emergency that requires urgent treatment with glucocorticoids to prevent acute adrenal crisis and circulatory collapse.

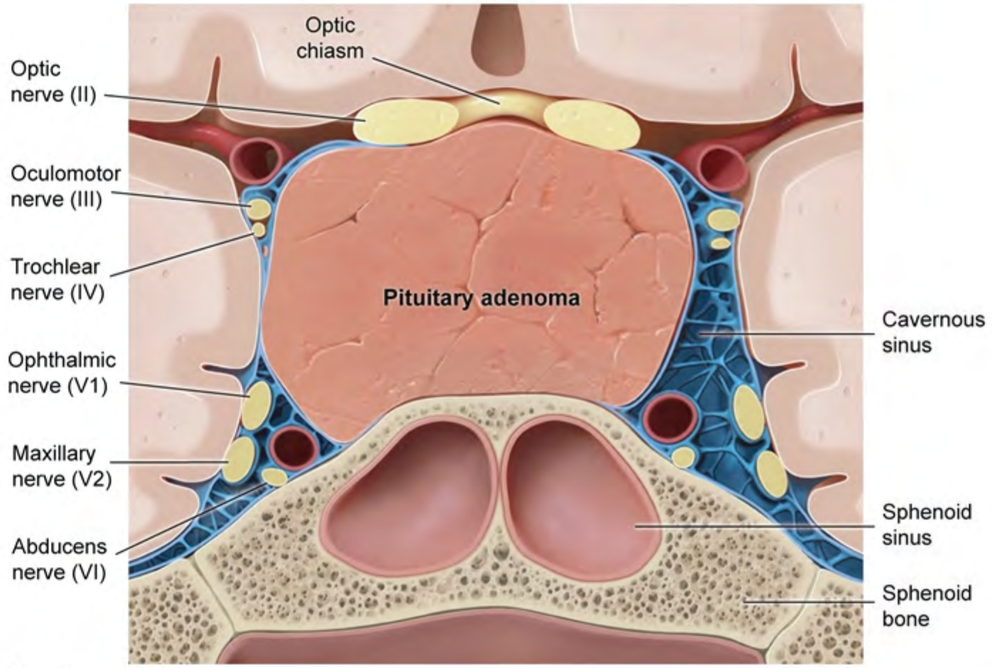
Pathology	Endocrine, Diabetes & Metabolism	Pituitary apoplexy
Subject	System	Topic

https://t.me/USMLEWorldStep1

Complications	• Severe hypotension (central adrenal

Exhibit Display

Cranial nerve compression by pituitary adenoma



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

This p
bitemp
the oc
patien
on cro

Pituita
crisis
vasoc
cease
medic

(Choi
minute
cortic

(Choi
(partia
hypert

(Choi
presen
activat
chiasm
of dec

(Choi
oral contraceptive use, malignancy, or infection. Presenting features include progressively worse headaches,

https://t.me/USMLEWorldStep1

Complications	• Severe hypotension (central adrenal

Exhibit Display

Pituitary apoplexy



©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

This p
bitem
the oc
patien
on cro

Pituita
crisis
vasoc
cease
medic

(Choi
minute
cortic

(Choi
(partia
hypert

(Choi
preser
activat
chiasn
of dec

(Choi
oral contraceptive use, malignancy, or infection. Presenting features include progressively worse headaches,

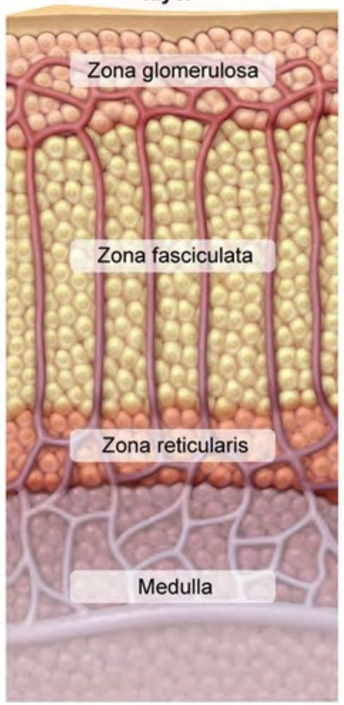
https://t.me/USMLEWorldStep1

Complications	• Severe hypotension (central adrenal

Exhibit Display

Adrenal cortical structure & function

Principal stimulatory hormone	Adrenal layer	Principal secreted hormone	Physiologic effect
Angiotensin II	Zona glomerulosa	Aldosterone	↑ Blood volume
ACTH	Zona fasciculata	Cortisol	↑ Vascular tone ↑ Blood glucose
ACTH	Zona reticularis	Androgens	Libido & pubic hair in women
	Medulla		



©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

This p
bitem
the oc
patien
on cro

Pituita
crisis
vasoc
cease
medic

(Choi
minute
cortic

(Choi
(partia
hypert

(Choi
preser
activat
chiasn
of dec

(Choi

oral contraceptive use, malignancy, or infection. Presenting features include progressively worse headaches,

https://t.me/USMLEWorldStep1

This patient had typical features of acute pituitary hemorrhage (**pituitary apoplexy**), including a severe **headache**,

bitem
the oc
patien
on cro

Pituita
crisis
vasoc
cease
medic

(Choi
minute
cortic

(Choi
(partia
hypert

(Choi
preser
activat
chiasm
of dec

(Choi
oral co
vomiti
decrea

Educational objective:

Exhibit Display

Pituitary apoplexy



©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

A 32-year-old man comes to the office due to vision problems. Over the last 6 weeks, he has had several "near-misses" while driving, having been nearly hit by cars coming from both the right and left sides. He also reports frequent headaches. The patient has no prior medical conditions and takes no medications. He does not use tobacco, alcohol, or illicit drugs. Physical examination reveals deficits in the bilateral temporal visual fields. Extraocular movements are bilaterally intact, and the remainder of the neurological examination shows no abnormalities. Which of the following additional findings is most likely to be present in this patient?

- A. Decreased libido
- B. Enlarged jaw bone
- C. Excessive urination
- D. Heat intolerance
- E. Skin hyperpigmentation
- F. Skin thinning

Submit

https://t.me/USMLEWorldStep1

A 32-year-old man comes to the office due to vision problems. Over the last 6 weeks, he has had several "near-misses" while driving, having been nearly hit by cars coming from both the right and left sides. He also reports frequent headaches. The patient has no prior medical conditions and takes no medications. He does not use tobacco, alcohol, or illicit drugs. Physical examination reveals deficits in the bilateral temporal visual fields. Extraocular movements are bilaterally intact, and the remainder of the neurological examination shows no abnormalities. Which of the following additional findings is most likely to be present in this patient?

- ✓ A. Decreased libido (81%)
- B. Enlarged jaw bone (5%)
- C. Excessive urination (3%)
- D. Heat intolerance (2%)
- E. Skin hyperpigmentation (4%)
- F. Skin thinning (1%)

Correct

81% Answered correctly

03 secs Time Spent

2023 Version

Explanation

Pituitary adenomas	
Cell type	**Clinical features of tumor**
Lactotroph (prolactin)	• Hypogonadism, infertility (men) • Galactorrhea, amenorrhea (women)
Corticotroph	

https://t.me/USMLEWorldStep1

Pituitary adenomas	
Cell type	**Clinical features of tumor**
Lactotroph (prolactin)	• Hypogonadism, infertility (men) • Galactorrhea, amenorrhea (women)
Corticotroph (ACTH)	• Cushing disease
Somatotroph (growth hormone)	• Acromegaly (adults) • Gigantism (children)
Thyrotroph (TSH)	• Thyrotoxicosis
Gonadotroph (LH, FSH)	• Nonfunctioning (hypopituitarism) • Mass effect

This patient's symptoms are worrisome for a **pituitary tumor**. Large tumors can cause **headaches** due to mass effect, and compression of the optic chiasm by suprasellar extension of the tumor can cause **bitemporal hemianopsia**. These tumors can also cause loss of normal pituitary function by compression of surrounding cells. Pituitary adenomas typically arise from 1 of the 5 major cell types of the anterior pituitary; physiologic symptoms depend on the hormones produced by the tumor. The most common hormonally active (functional) adenomas are prolactin-secreting adenomas (**prolactinomas**).

Prolactin is a peptide hormone whose primary action is maintenance of lactation in the postpartum period; prolactinomas classically cause galactorrhea in premenopausal women. Prolactin also suppresses GnRH production from the hypothalamus, which in women leads to amenorrhea and in men causes **hypogonadism** (eg, impotence, **decreased libido**, infertility). Because the symptoms of hyperprolactinemia in men and postmenopausal women are often mild and nonspecific, patients may not seek care until the tumors are large and

https://t.me/USMLEWorldStep1

(LH, FSH) | Mass effect

This patient's symptoms are worrisome for a **pituitary tumor**. Large tumors can cause **headaches** due to mass effect, and compression of the optic chiasm by suprasellar extension of the tumor can cause **bitemporal hemianopsia**. These tumors can also cause loss of normal pituitary function by compression of surrounding cells. Pituitary adenomas typically arise from 1 of the 5 major cell types of the anterior pituitary; physiologic symptoms depend on the hormones produced by the tumor. The most common hormonally active (functional) adenomas are prolactin-secreting adenomas (**prolactinomas**).

Prolactin is a peptide hormone whose primary action is maintenance of lactation in the postpartum period; prolactinomas classically cause galactorrhea in premenopausal women. Prolactin also suppresses GnRH production from the hypothalamus, which in women leads to amenorrhea and in men causes **hypogonadism** (eg, impotence, **decreased libido**, infertility). Because the symptoms of hyperprolactinemia in men and postmenopausal women are often mild and nonspecific, patients may not seek care until the tumors are large and cause mass effect symptoms.

(Choices B, D, and F) Somatotroph (growth hormone-secreting) adenomas can present with gigantism (in children) or acromegaly in adults. Thyrotroph (TSH-secreting) adenomas cause central hyperthyroidism (eg, heat intolerance, tachycardia). Thinning of the skin, typically manifesting as abdominal stria, is a characteristic feature of Cushing syndrome; when hypercortisolism is due to a corticotroph (ACTH-producing) adenoma, it is referred to as Cushing disease. These tumors are significantly less common than prolactinomas.

(Choice C) Mass lesions involving the pituitary stalk or posterior pituitary could cause headaches and bitemporal hemianopsia in addition to central diabetes insipidus (due to decreased release of antidiuretic hormone [ADH] from the posterior pituitary). However, polyuria is typically only transient (lasting <6 weeks) because the hypothalamus is able to bypass the pituitary and directly release ADH into the circulation.

(Choice E) Hyperpigmentation in the context of pituitary disease is typically due to hypersecretion of ACTH, either due to a corticotroph adenoma or in response to primary adrenal insufficiency.

Educational objective:
Pituitary tumors can present with headaches, bitemporal hemianopsia, and hypopituitarism; the most common hormonally active (functional) adenomas are prolactin-secreting adenomas (prolactinomas). Prolactinomas can

https://t.me/USMLEWorldStep1

hemianopsia. These tumors can also cause loss of normal pituitary function by compression of surrounding cells. Pituitary adenomas typically arise from 1 of the 5 major cell types of the anterior pituitary; physiologic symptoms depend on the hormones produced by the tumor. The most common hormonally active (functional) adenomas are prolactin-secreting adenomas (**prolactinomas**).

Prolactin is a peptide hormone whose primary action is maintenance of lactation in the postpartum period; prolactinomas classically cause galactorrhea in premenopausal women. Prolactin also suppresses GnRH production from the hypothalamus, which in women leads to amenorrhea and in men causes **hypogonadism** (eg, impotence, **decreased libido**, infertility). Because the symptoms of hyperprolactinemia in men and postmenopausal women are often mild and nonspecific, patients may not seek care until the tumors are large and cause mass effect symptoms.

(Choices B, D, and F) Somatotroph (growth hormone-secreting) adenomas can present with gigantism (in children) or acromegaly in adults. Thyrotroph (TSH-secreting) adenomas cause central hyperthyroidism (eg, heat intolerance, tachycardia). Thinning of the skin, typically manifesting as abdominal stria, is a characteristic feature of Cushing syndrome; when hypercortisolism is due to a corticotroph (ACTH-producing) adenoma, it is referred to as Cushing disease. These tumors are significantly less common than prolactinomas.

(Choice C) Mass lesions involving the pituitary stalk or posterior pituitary could cause headaches and bitemporal hemianopsia in addition to central diabetes insipidus (due to decreased release of antidiuretic hormone [ADH] from the posterior pituitary). However, polyuria is typically only transient (lasting <6 weeks) because the hypothalamus is able to bypass the pituitary and directly release ADH into the circulation.

(Choice E) Hyperpigmentation in the context of pituitary disease is typically due to hypersecretion of ACTH, either due to a corticotroph adenoma or in response to primary adrenal insufficiency.

Educational objective:
Pituitary tumors can present with headaches, bitemporal hemianopsia, and hypopituitarism; the most common hormonally active (functional) adenomas are prolactin-secreting adenomas (prolactinomas). Prolactinomas can cause galactorrhea and amenorrhea in women. In men, they often present with hypogonadism.

References

- Progress in the diagnosis and classification of pituitary adenomas.

https://t.me/USMLEWorldStep1

(LH, FSH) | Mass effect

This patient's symptoms are worrisome for a **pituitary tumor**. Large tumors can cause **headaches** due to mass effect, **hemia**
Pituita
depen
prolac

Prolac
prolac
produc
impote
postm
cause

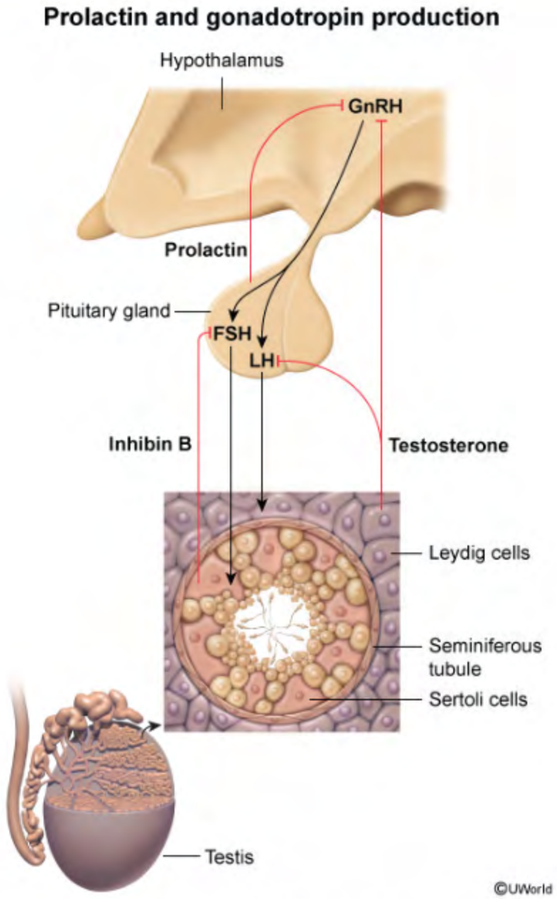
(Choi
childre
intoler
of Cus
as Cus

(Choi
hemia
the po
is able

(Choi
due to

Educa
Pituitary tumors can present with headaches, bitemporal hemianopsia, and hypopituitarism; the most common hormonally active (functional) adenomas are prolactin-secreting adenomas (prolactinomas). Prolactinomas can

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

(LH, FSH)	• Mass effect

This patient's symptoms are worrisome for a **pituitary tumor**. Large tumors can cause **headaches** due to mass effect, **hemia**
Pituita
depen
prolac

Prolac
prolac
produc
impote
postm
cause

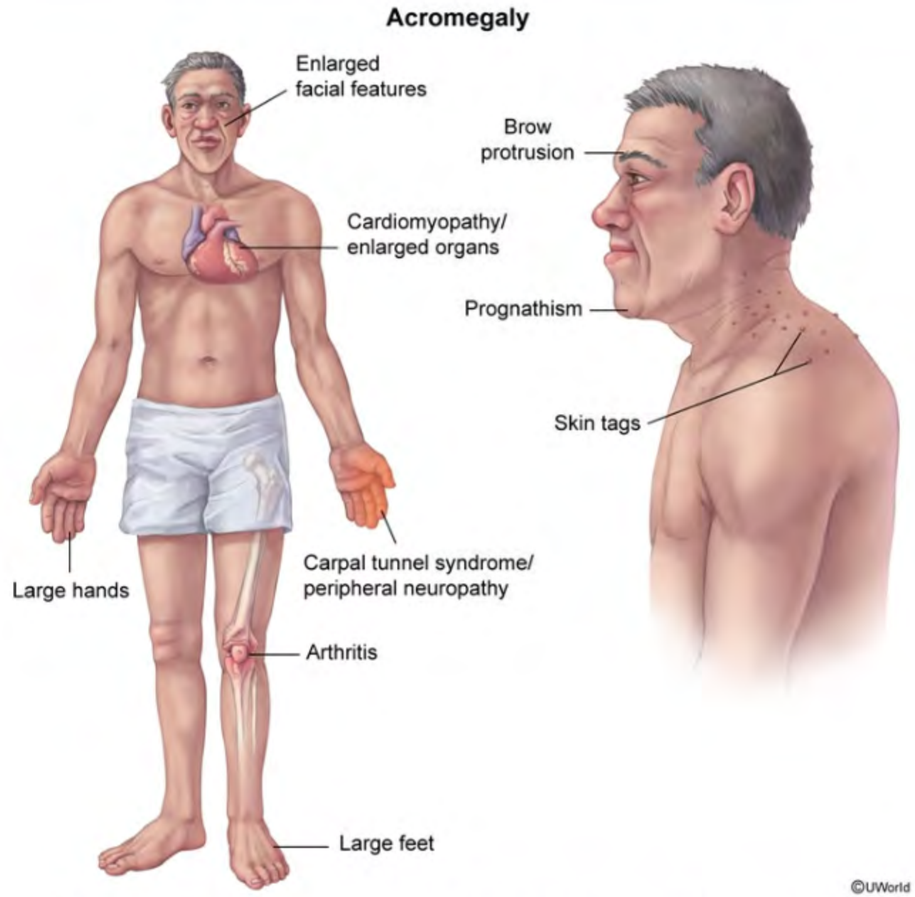
(Choi
childre
intoler
of Cus
as Cus

(Choi
hemia
the po
is able

(Choi
due to

Educa
Pituitary tumors can present with headaches, bitemporal hemianopsia, and hypopituitarism; the most common hormonally active (functional) adenomas are prolactin-secreting adenomas (prolactinomas). Prolactinomas can

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

(EH, PGH) | Mass effect

This patient's symptoms are worrisome for a **pituitary tumor**. Large tumors can cause **headaches** due to mass effect, **hemia**
Pituita
depen
prolac

Prolac
prolac
produc
impote
postm
cause

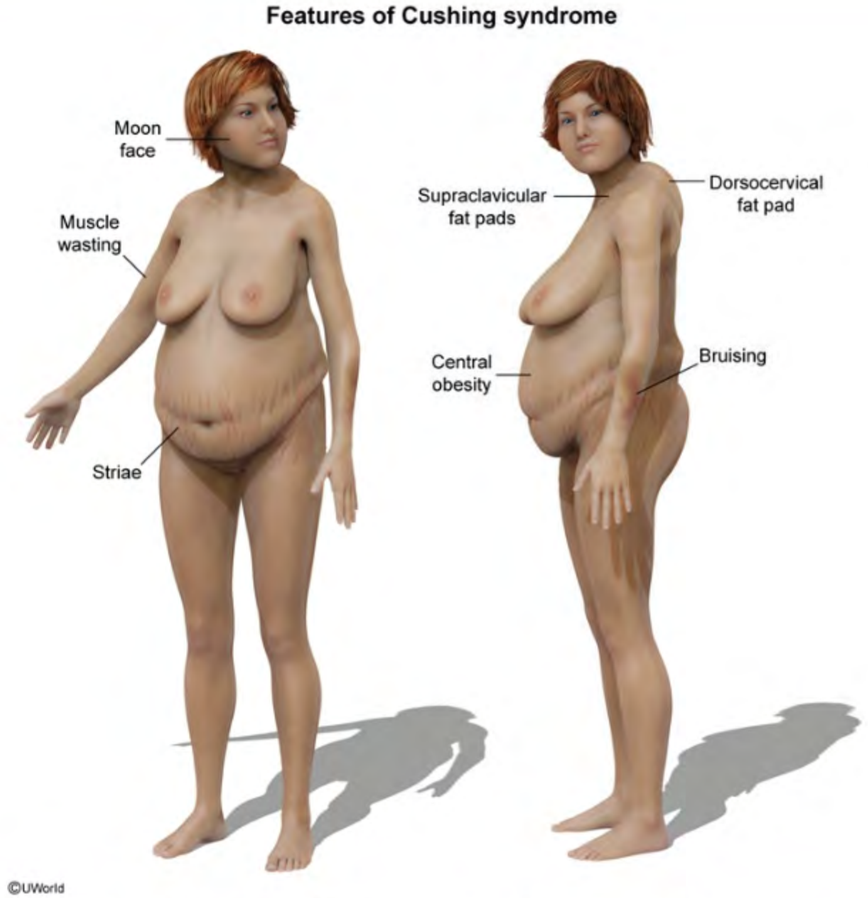
(Choi
childre
intoler
of Cus
as Cus

(Choi
hemia
the po
is able

(Choi
due to

Educa
Pituitary tumors can present with headaches, bitemporal hemianopsia, and hypopituitarism; the most common hormonally active (functional) adenomas are prolactin-secreting adenomas (prolactinomas). Prolactinomas can

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

A patient is treated with a gonadotropin-releasing hormone (GnRH) infusion. An intravenous line is placed and connected to a reservoir through a computerized pump. The pump is programmed to deliver a predetermined dose of GnRH every 90 minutes, which results in a sharp rise in serum GnRH levels with each dose, followed by a rapid return to baseline. LH and FSH levels are monitored in the initial phase of treatment. Which of the following is the most likely indication for using this GnRH infusion?

- A. Breast cancer
- B. Endometriosis
- C. Infertility
- D. Precocious puberty
- E. Prostate cancer

Submit

https://t.me/USMLEWorldStep1

A patient is treated with a gonadotropin-releasing hormone (GnRH) infusion. An intravenous line is placed and connected to a reservoir through a computerized pump. The pump is programmed to deliver a predetermined dose of GnRH every 90 minutes, which results in a sharp rise in serum GnRH levels with each dose, followed by a rapid return to baseline. LH and FSH levels are monitored in the initial phase of treatment. Which of the following is the most likely indication for using this GnRH infusion?

- A. Breast cancer (0%)
- ✗ B. Endometriosis (1%)
- ✓ C. Infertility (87%)
- D. Precocious puberty (4%)
- E. Prostate cancer (4%)

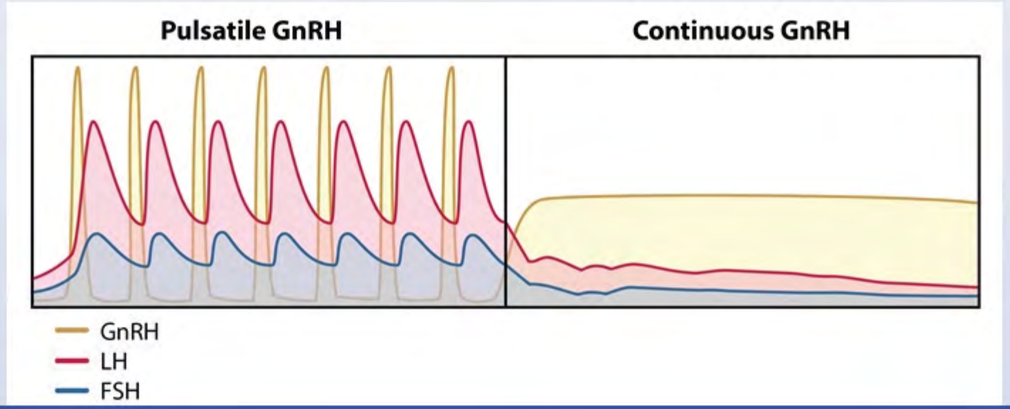
Incorrect
Correct answer
C

87%
Answered correctly

04 secs
Time Spent

2023
Version

Explanation



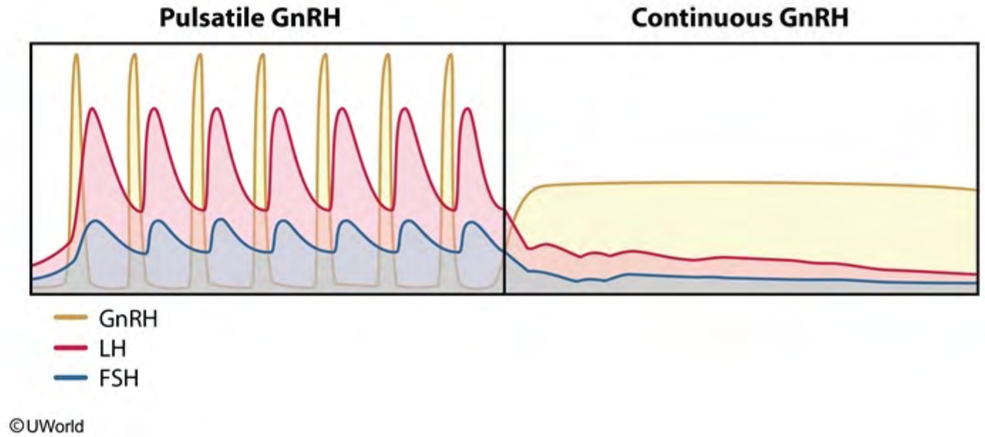
https://t.me/USMLEWorldStep1

A patient is treated with a gonadotropin-releasing hormone (GnRH) infusion. An intravenous line is placed and
conne
of GnR
return
most li

Incc
Corre
C

Expl

Exhibit Display



Zoom In Zoom Out Reset New | Existing My Notebook

LH
FSH

https://t.me/USMLEWorldStep1

Gonadotropin-releasing hormone (GnRH) is a polypeptide that is normally released from the anterior hypothalamus in a pulsatile manner. GnRH is carried to the anterior pituitary via the portal circulation, where it stimulates FSH and LH production. **Pulsatile** stimulation of pituitary gonadotrophin cells by GnRH leads to upregulation of GnRH receptors and enhanced FSH and LH secretion. FSH and LH are responsible for development of the dominant follicle in the ovaries. Optimal frequency and amplitude of GnRH pulses are crucial for FSH and LH release and subsequent ovulation.

Anovulation due to hypogonadotropic hypogonadism is a common form of **infertility** that can be treated by pulsatile administration of GnRH. GnRH has a very short half-life and is given by a programmable pump that delivers a predetermined dose at physiologic intervals. Ovulation occurs in most patients in 10-20 days. Signs of ovulation include loss of a dominant follicle on ultrasound, surge in urine LH levels, rise in serum progesterone levels, and rise in basal body temperature.

(Choices A, B, D, and E) Constant, rather than pulsatile, GnRH activity causes down-regulation of the GnRH receptors on pituitary gonadotrophin cells, which suppresses LH and FSH secretion. Although it is possible to use a pump to administer GnRH at a steady rate, it has a very short half-life, and long-acting GnRH analogs (eg, leuprolide) are easier to use and can be given monthly by intramuscular injection. Long-acting GnRH analog therapy is used when suppression of gonadal function is desired, such as in certain patients with prostate cancer, endometriosis, precocious puberty, or premenopausal breast cancer.

Educational objective:
Pulsatile administration of gonadotropin-releasing hormone (GnRH) stimulates FSH and LH release and is useful for the treatment of infertility. Nonpulsatile (constant) infusion of GnRH, or a long-acting analog, suppresses FSH and LH release and subsequently suppresses gonadal function.

References

- Use of gonadotropin-releasing hormone agonists to trigger ovulation.

Physiology	Endocrine, Diabetes & Metabolism	Infertility
Subject	System	Topic

Copyright © UWorld. All rights reserved.

https://t.me/USMLEWorldStep1

A 68-year-old man reports myalgia and fatigue during a follow-up office visit. The patient has been taking high-intensity statin therapy since he had an acute myocardial infarction several weeks ago. His other medical problems include hypertension and type 2 diabetes mellitus. On examination, there is mild generalized muscle tenderness. Serum creatine kinase level is 456 U/L. Vitamin D and TSH levels are within normal range. The patient's statin therapy is discontinued, and he is started on a medication that inhibits cholesterol absorption at the brush border of the small intestine. Which of the following drugs was most likely started in this patient?

- A. Colesevelam
- B. Ezetimibe
- C. Fenofibrate
- D. Nicotinic acid
- E. PCSK9 inhibitor

Submit

https://t.me/USMLEWorldStep1

A 68-year-old man reports myalgia and fatigue during a follow-up office visit. The patient has been taking high-intensity statin therapy since he had an acute myocardial infarction several weeks ago. His other medical problems include hypertension and type 2 diabetes mellitus. On examination, there is mild generalized muscle tenderness. Serum creatine kinase level is 456 U/L. Vitamin D and TSH levels are within normal range. The patient's statin therapy is discontinued, and he is started on a medication that inhibits cholesterol absorption at the brush border of the small intestine. Which of the following drugs was most likely started in this patient?

- ✗ A. Colesevelam (9%)
- ✓ B. Ezetimibe (77%)
- C. Fenofibrate (10%)
- D. Nicotinic acid (1%)
- E. PCSK9 inhibitor (2%)

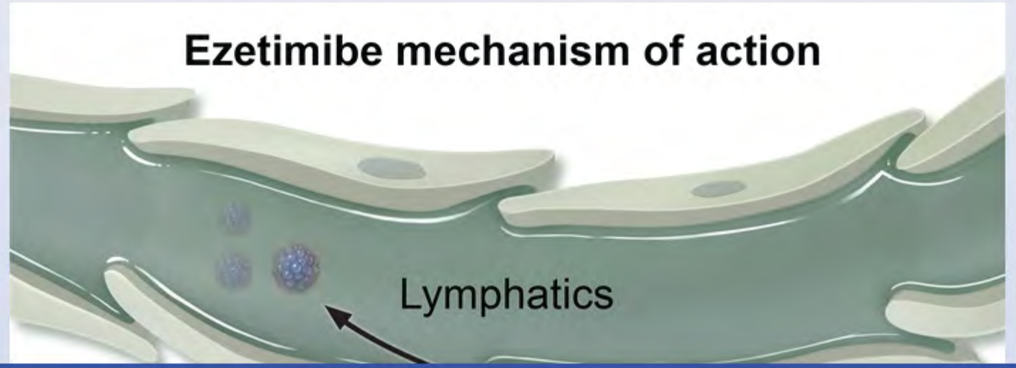
Incorrect
Correct answer
B

77%
Answered correctly

03 secs
Time Spent

2023
Version

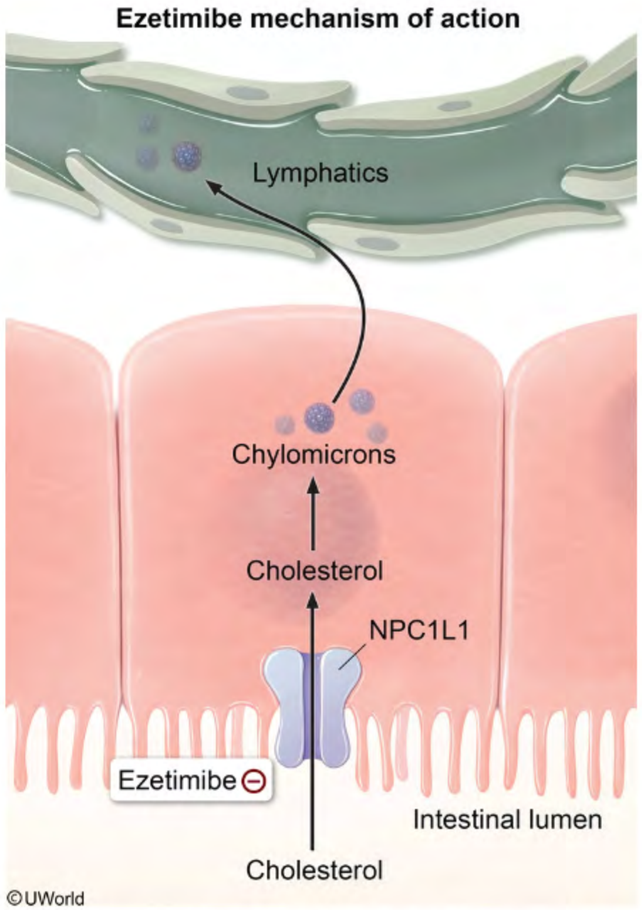
Explanation



https://t.me/USMLEWorldStep1

A 68-year-old man reports myalgia and fatigue during a follow-up office visit. The patient has been taking high-
intensi
proble
tender
patien
brush

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

©UWorld

Cholesterol-lowering agents commonly work in 1 of 3 ways:

- Decreasing hepatic cholesterol synthesis
- Decreasing intestinal cholesterol absorption
- Altering cholesterol transport between the blood and tissues

Ezetimibe decreases **intestinal absorption** of cholesterol by inhibiting the Niemann-Pick C1-like 1 (NPC1L1) transporter protein, which transports dietary cholesterol from the gastrointestinal lumen into intestinal enterocytes. As a result, the total amount of dietary cholesterol reaching the liver decreases, lowering intrahepatocyte cholesterol levels. To compensate, the liver increases LDL receptor expression, which draws cholesterol out of the circulation.

(Choice A) Bile acid sequestrants (eg, colesevelam) bind bile salts in the intestine, decreasing their reabsorption. Subsequent depletion of the bile acid pool causes upregulation of cholesterol 7-α-hydroxylase, which converts cholesterol into bile acids.

(Choice C) Fibrates activate peroxisome proliferator-activated receptor-alpha transcription factors, which leads to stimulation of lipoprotein lipase activity and a decrease in triglyceride levels.

(Choice D) Nicotinic acid inhibits hepatic triglyceride synthesis, which in turn reduces the liver's availability to synthesize VLDL particles that are subsequently metabolized into LDL in the circulation.

(Choice E) Proprotein convertase subtilisin kexin 9 (PCSK9) increases degradation of hepatic LDL receptors. Alirocumab is a monoclonal antibody against PCSK9 that blocks this effect, resulting in increased availability of LDL receptors on hepatocyte membranes and subsequently increased clearance of LDL from the blood.

Educational objective:
Ezetimibe reduces intestinal absorption of cholesterol. As a result, the amount of dietary cholesterol reaching the liver decreases. To compensate, the liver increases LDL receptor expression, which draws cholesterol out of the circulation.

References

- Ezetimibe--a new approach in hypercholesterolemia management

https://t.me/USMLEWorldStep1

©UWorld

Exhibit Display

Antihyperlipidemic medications

Drug	Mechanism	Major lipid effects	Adverse effects
Statins	• Inhibit HMG-CoA reductase	• ↓↓ LDL • ↓ Triglycerides	• Hepatotoxicity • Muscle toxicity
Ezetimibe	• ↓ Intestinal cholesterol absorption	• ↓ LDL	• ↑ Hepatotoxicity if given with statins
Bile acid sequestrants	• Prevent reabsorption of bile acids in the intestine	• ↓ LDL	• Nausea, bloating, cramping • Impaired drug & fat-soluble vitamin absorption
Niacin	• ↓ Fatty acid release • ↓ VLDL synthesis • ↓ HDL clearance	• ↓ LDL • ↑↑ HDL	• Flushing & pruritus • Hepatotoxicity • Hyperuricemia/gout
Fibrates	• Activate PPAR-α • ↓ VLDL synthesis	• ↓↓ Triglycerides • ↑ HDL	• Muscle toxicity • Gallstones
Fish oil/ omega-3 fatty acids	• ↓ VLDL synthesis • ↓ Apolipoprotein B synthesis	• ↓ Triglycerides • ↑ HDL	• Fishy taste

PPAR-α = peroxisome proliferator-activated receptor-alpha.

New | Existing | My Notebook

References

- Ezetimibe--a new approach in hypercholesterolemia management

https://t.me/USMLEWorldStep1

©UWorld

Exhibit Display

Antihyperlipidemic medications

Drug	Mechanism	Major lipid effects	Adverse effects
Statins	• Inhibit HMG-CoA reductase	• ↓↓ LDL • ↓ Triglycerides	• Hepatotoxicity • Muscle toxicity
Ezetimibe	• ↓ Intestinal cholesterol absorption	• ↓ LDL	• ↑ Hepatotoxicity if given with statins
Bile acid sequestrants	• Prevent reabsorption of bile acids in the intestine	• ↓ LDL	• Nausea, bloating, cramping • Impaired drug & fat-soluble vitamin absorption
Niacin	• ↓ Fatty acid release • ↓ VLDL synthesis • ↓ HDL clearance	• ↓ LDL • ↑↑ HDL	• Flushing & pruritus • Hepatotoxicity • Hyperuricemia/gout
Fibrates	• Activate PPAR-α • ↓ VLDL synthesis	• ↓↓ Triglycerides • ↑ HDL	• Muscle toxicity • Gallstones
Fish oil/ omega-3 fatty acids	• ↓ VLDL synthesis • ↓ Apolipoprotein B synthesis	• ↓ Triglycerides • ↑ HDL	• Fishy taste

PPAR-α = peroxisome proliferator-activated receptor-alpha.

New | Existing | My Notebook

References

- Ezetimibe--a new approach in hypercholesterolemia management

https://t.me/USMLEWorldStep1

A 52-year-old woman comes to the office for follow-up of type 2 diabetes mellitus. The patient was diagnosed with diabetes 6 months ago and initiated intensive lifestyle modification with increased exercise and a calorie-restricted diet; since that time, she has felt better subjectively but has lost only 2 kg (4.4 lb). Vital signs are normal. BMI is 35 kg/m^2. Fasting glucose is 155 mg/dL and hemoglobin A1c is 8.0%. Serum renal and liver function markers are normal. After discussion with the patient, metformin therapy is initiated. Which of the following physiologic changes are most likely to result as a direct effect of this medication?

	Hepatic gluconeogenesis	Muscle glucose uptake	Endogenous insulin production
A.	Decreased	Increased	Increased
B.	Decreased	Increased	Unchanged
C.	Decreased	Unchanged	Unchanged
D.	Unchanged	Increased	Unchanged
E.	Unchanged	Unchanged	Increased

Submit

https://t.me/USMLEWorldStep1

A 52-year-old woman comes to the office for follow-up of type 2 diabetes mellitus. The patient was diagnosed with diabetes 6 months ago and initiated intensive lifestyle modification with increased exercise and a calorie-restricted diet; since that time, she has felt better subjectively but has lost only 2 kg (4.4 lb). Vital signs are normal. BMI is 35 kg/m^2. Fasting glucose is 155 mg/dL and hemoglobin A1c is 8.0%. Serum renal and liver function markers are normal. After discussion with the patient, metformin therapy is initiated. Which of the following physiologic changes are most likely to result as a direct effect of this medication?

		Hepatic gluconeogenesis	Muscle glucose uptake	Endogenous insulin production	
✗	A.	Decreased	Increased	Increased	(15%)
✓	B.	Decreased	Increased	Unchanged	(63%)
	C.	Decreased	Unchanged	Unchanged	(15%)
	D.	Unchanged	Increased	Unchanged	(4%)
	E.	Unchanged	Unchanged	Increased	(1%)

Incorrect
Correct answer
B

63%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

Metformin	
Mechanism of action	• Inhibits mitochondrial glycerophosphate dehydrogenase • Upregulates AMP-activated protein kinase
	↓ Hepatic glucose production

https://t.me/USMLEWorldStep1

Metformin	
Mechanism of action	• Inhibits mitochondrial glycerophosphate dehydrogenase • Upregulates AMP-activated protein kinase
Metabolic effects	• ↓ Hepatic glucose production • ↓ Intestinal glucose absorption • ↑ Peripheral glucose uptake/utilization • ↓ Lipogenesis
Pharmacokinetics	• Renal clearance • No significant metabolites
Adverse effects	• Diarrhea • Lactic acidosis • Vitamin B_{12} deficiency
Precautions/ contraindications	• Renal insufficiency (check serum creatinine) • Hepatic insufficiency • Decompensated heart failure

This patient has uncontrolled type 2 diabetes mellitus and is appropriately given metformin, which is the preferred first-line medication for most patients. **Metformin** has a number of important metabolic effects:

- **Reduced hepatic gluconeogenesis**: metformin inhibits mitochondrial glycerophosphate dehydrogenase, which reduces the availability of substrates for gluconeogenesis (eg, glycerol, lactate).
- **Increased** insulin-dependent **peripheral glucose uptake** and utilization.
- Reduced circulating lipid levels: metformin upregulates AMP-activated protein kinase in hepatocytes, which inhibits lipogenesis.

Circulating levels of endogenous insulin are unchanged or slightly decreased by metformin; therefore, metformin carries **low risk of hypoglycemia**. In addition, it reduces caloric intake due to decreased appetite and decreased

https://t.me/USMLEWorldStep1

	• Vitamin B_{12} deficiency
Precautions/ contraindications	• Renal insufficiency (check serum creatinine) • Hepatic insufficiency • Decompensated heart failure

This patient has uncontrolled type 2 diabetes mellitus and is appropriately given metformin, which is the preferred first-line medication for most patients. **Metformin** has a number of important metabolic effects:

- **Reduced hepatic gluconeogenesis**: metformin inhibits mitochondrial glycerophosphate dehydrogenase, which reduces the availability of substrates for gluconeogenesis (eg, glycerol, lactate).
- **Increased** insulin-dependent **peripheral glucose uptake** and utilization.
- Reduced circulating lipid levels: metformin upregulates AMP-activated protein kinase in hepatocytes, which inhibits lipogenesis.

Circulating levels of endogenous insulin are unchanged or slightly decreased by metformin; therefore, metformin carries **low risk of hypoglycemia**. In addition, it reduces caloric intake due to decreased appetite and decreased absorption of glucose, leading to modest **weight loss** in most patients.

(Choice A) Sulfonylureas (eg, glyburide, glimepiride) stimulate beta cell insulin release, leading to decreased glycogenolysis and gluconeogenesis and increased peripheral uptake of glucose; the higher circulating insulin levels also confer an increased risk of hypoglycemia and weight gain.

Educational objective:
Metformin reduces hepatic gluconeogenesis and release of glucose into circulation; increases peripheral glucose uptake and utilization; and reduces circulating lipid levels. Circulating insulin levels are unchanged or slightly decreased; therefore, metformin carries low risk of hypoglycemia. In addition, metformin reduces caloric intake due to decreased appetite and decreased absorption of glucose, leading to modest weight loss.

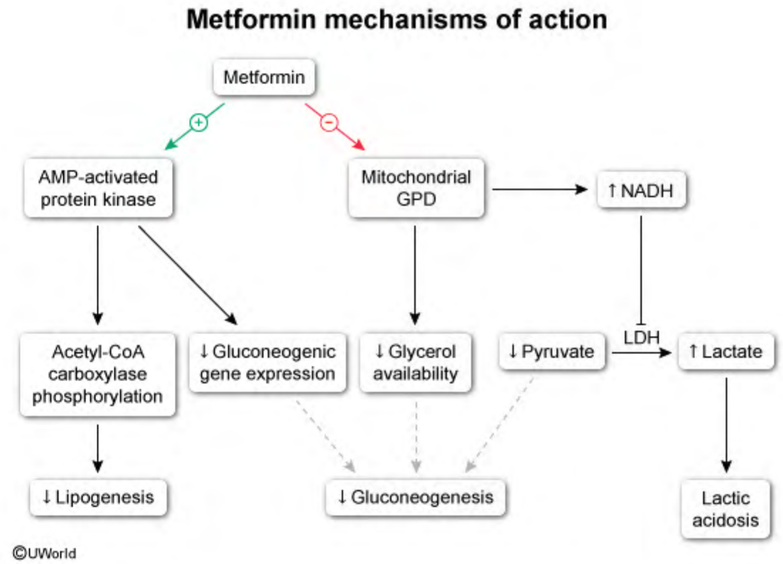
Pharmacology	Endocrine, Diabetes & Metabolism	Diabetes mellitus
Subject	System	Topic

Copyright © UWorld. All rights reserved.

https://t.me/USMLEWorldStep1

- Vitamin B_{12} deficiency

Exhibit Display



Zoom In Zoom Out Reset New | Existing My Notebook

This p
first-lin
- R
- In
- R

Circula
carries
absorp

(Choi
glycog
levels

Educa
Metfor
uptake
decrea
due to

Pharma
Subject

Copyright © UWorld. All rights reserved.

https://t.me/USMLEWorldStep1

A 65-year-old man comes to the office due to advanced prostate cancer with bone metastases. For the last 4 months, he has been treated with a GnRH agonist, which has significantly reduced his bone pain. However, the patient now reports discomfort at the anterior chest wall. Physical examination reveals bilateral, mildly tender enlargement of the breast tissue behind the nipple-areolar complex. Early initiation of which of the following medications would be most appropriate for preventing this patient's breast symptoms?

- A. Bicalutamide
- B. Danazol
- C. Finasteride
- D. Spironolactone
- E. Tamoxifen

Submit

https://t.me/USMLEWorldStep1

A 65-year-old man comes to the office due to advanced prostate cancer with bone metastases. For the last 4 months, he has been treated with a GnRH agonist, which has significantly reduced his bone pain. However, the patient now reports discomfort at the anterior chest wall. Physical examination reveals bilateral, mildly tender enlargement of the breast tissue behind the nipple-areolar complex. Early initiation of which of the following medications would be most appropriate for preventing this patient's breast symptoms?

- A. Bicalutamide (13%)
- ✗ B. Danazol (17%)
- C. Finasteride (11%)
- D. Spironolactone (8%)
- ✓ E. Tamoxifen (48%)

Incorrect
Correct answer
E

48%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

Gynecomastia	
Clinical findings	• Development of glandular breast tissue in males
Pathophysiology	• Increased estrogen/androgen ratio • Ductal epithelial hyperplasia & stromal fibrosis
Common etiologies	• Increased estrogen levels (eg, cirrhosis, obesity) • Decreased testosterone levels (eg, chronic kidney disease, hypogonadism) • Medication effect ◦ Decreased androgen production (eg, GnRH agonists, ketoconazole)

https://t.me/USMLEWorldStep1

Explanation

Gynecomastia	
Clinical findings	• Development of glandular breast tissue in males
Pathophysiology	• Increased estrogen/androgen ratio • Ductal epithelial hyperplasia & stromal fibrosis
Common etiologies	• Increased estrogen levels (eg, cirrhosis, obesity) • Decreased testosterone levels (eg, chronic kidney disease, hypogonadism) • Medication effect ◦ Decreased androgen production (eg, GnRH agonists, ketoconazole) ◦ Decreased conversion to dihydrotestosterone (eg, 5-alpha reductase inhibitors) ◦ Inhibition of androgen receptors (eg, spironolactone, bicalutamide)

Gynecomastia is the development of glandular breast tissue in males. It is characterized by **ductal epithelial hyperplasia** with fibrosis of the surrounding stroma. Breast growth is inhibited by androgens and promoted by estrogens; conditions that **increase the estrogen to androgen ratio** can lead to gynecomastia. Common pathologic causes include cirrhosis (increased aromatase activity, decreased clearance of estrogens), end-stage renal disease (decreased testosterone production), and medications (eg, spironolactone, ketoconazole).

Men with prostate cancer who receive **androgen-deprivation therapy** (eg, orchiectomy, long-acting GnRH agonists, androgen receptor inhibitors) can develop gynecomastia due to dramatic (>95%) reductions in circulating testosterone (with lesser reductions in estrogens). Treatment with **tamoxifen**, a selective estrogen receptor modulator that acts as an estrogen antagonist in the breast, can reduce the risk of gynecomastia in these patients.

(Choice A) Bicalutamide is a testosterone receptor antagonist used in the treatment of prostate cancer. This drug can cause or worsen gynecomastia due to the reduced physiologic testosterone effect.

(Choice B) Danazol is a synthetic steroid with androgenic and antiestrogenic effects. It may improve gynecomastia in patients with hypogonadism but can lead to rapid growth of prostate cancer and would not be

https://t.me/USMLEWorldStep1

- Inhibition of androgen receptors (eg, spironolactone, bicalutamide)

Gynecomastia is the development of glandular breast tissue in males. It is characterized by **ductal epithelial hyperplasia** with fibrosis of the surrounding stroma. Breast growth is inhibited by androgens and promoted by estrogens; conditions that **increase the estrogen to androgen ratio** can lead to gynecomastia. Common pathologic causes include cirrhosis (increased aromatase activity, decreased clearance of estrogens), end-stage renal disease (decreased testosterone production), and medications (eg, spironolactone, ketoconazole).

Men with prostate cancer who receive **androgen-deprivation therapy** (eg, orchiectomy, long-acting GnRH agonists, androgen receptor inhibitors) can develop gynecomastia due to dramatic (>95%) reductions in circulating testosterone (with lesser reductions in estrogens). Treatment with **tamoxifen**, a selective estrogen receptor modulator that acts as an estrogen antagonist in the breast, can reduce the risk of gynecomastia in these patients.

(Choice A) Bicalutamide is a testosterone receptor antagonist used in the treatment of prostate cancer. This drug can cause or worsen gynecomastia due to the reduced physiologic testosterone effect.

(Choice B) Danazol is a synthetic steroid with androgenic and antiestrogenic effects. It may improve gynecomastia in patients with hypogonadism but can lead to rapid growth of prostate cancer and would not be appropriate for this patient.

(Choices C and D) Finasteride is a 5-α reductase inhibitor that reduces the conversion of testosterone to dihydrotestosterone; it is used for treatment of benign prostatic hyperplasia and male-pattern hair loss. Spironolactone is an aldosterone antagonist that also decreases testosterone production and inhibits the testosterone receptor; it is commonly used for heart failure, cirrhosis, and hypertension. Both of these agents are associated with increased risk of gynecomastia.

Educational objective:
Gynecomastia is the development of glandular breast tissue in males and is commonly seen in men receiving androgen deprivation therapy for prostate cancer. Tamoxifen inhibits the effect of estrogen on breast tissue and can reduce the risk of gynecomastia in these patients.

Pharmacology	Endocrine, Diabetes & Metabolism	Gynecomastia
Subject	System	Topic

https://t.me/USMLEWorldStep1

A 45-year-old man comes to the office due to a 3-month history of dull, aching, daily headaches and peripheral vision loss. He also has erectile dysfunction and loss of libido. The patient has no known chronic medical conditions and takes no medications. Blood pressure is 120/70 mm Hg and pulse is 80/min. BMI is 27 kg/m^2. Examination shows bilateral gynecomastia and bitemporal hemianopsia. Serum laboratory test results are as follows:

Creatinine	1.2 mg/dL
TSH	1.1 μU/mL
Cortisol	12 μg/dL
Prolactin	332 ng/mL

MRI reveals a 1.3-cm pituitary macroadenoma. Cabergoline therapy is prescribed. Which of the following changes are most likely to occur in the first few weeks following initiation of therapy?

	Serum prolactin	Erectile dysfunction	Visual field defect
○ A.	Decrease	Improve	Improve
○ B.	Decrease	Improve	Worsen
○ C.	Decrease	No change	No change
○ D.	Increase	Improve	Improve
○ E.	Increase	Improve	No change

Submit

https://t.me/USMLEWorldStep1

A 45-year-old man comes to the office due to a 3-month history of dull, aching, daily headaches and peripheral vision loss. He also has erectile dysfunction and loss of libido. The patient has no known chronic medical conditions and takes no medications. Blood pressure is 120/70 mm Hg and pulse is 80/min. BMI is 27 kg/m^2. Examination shows bilateral gynecomastia and bitemporal hemianopsia. Serum laboratory test results are as follows:

Creatinine	1.2 mg/dL
TSH	1.1 µU/mL
Cortisol	12 µg/dL
Prolactin	332 ng/mL

MRI reveals a 1.3-cm pituitary macroadenoma. Cabergoline therapy is prescribed. Which of the following changes are most likely to occur in the first few weeks following initiation of therapy?

		Serum prolactin	Erectile dysfunction	Visual field defect	
✓	A.	Decrease	Improve	Improve	(64%)
	B.	Decrease	Improve	Worsen	(8%)
	C.	Decrease	No change	No change	(23%)
	D.	Increase	Improve	Improve	(1%)
	E.	Increase	Improve	No change	(2%)

Correct

64%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

https://t.me/USMLEWorldStep1

Prolactinoma	
Clinical features	• **Premenopausal women**: oligomenorrhea/amenorrhea, infertility, galactorrhea, hot flashes, decreased bone density • **Postmenopausal women**: mass-effect symptoms (headache, visual field defects) • **Men**: infertility, decreased libido, impotence, gynecomastia
Laboratory/ imaging	• Serum prolactin (often >200 ng/mL) • Tests to rule out renal insufficiency (creatinine) & hypothyroidism (TSH, thyroxine) • MRI of the head/pituitary
Treatment	• Dopamine agonist (cabergoline) • Transsphenoidal surgery

This patient has a prolactin-secreting pituitary adenoma (**prolactinoma**), confirmed with elevated serum prolactin and a pituitary mass visible on MRI. Prolactin can cause **hypogonadism** (eg, decreased libido, erectile dysfunction, gynecomastia) due to suppression of hypothalamic GnRH production. **Mass-effect symptoms** of the tumor commonly include headaches and visual field defects due to compression of the optic chiasm.

Unlike most pituitary hormones, which are under positive regulation by releasing hormones (eg, GnRH, TRH) from the hypothalamus, prolactin is primarily under negative regulation by dopaminergic neurons via the pituitary stalk. **Dopamine agonists** (eg, **cabergoline**, bromocriptine) are used in patients with prolactinomas to **suppress prolactin production** and **reduce tumor size**.

Prolactin levels typically fall significantly within the first **2-3 weeks** of therapy **(Choices D and E)**, with a corresponding improvement in hypogonadal symptoms. Although decreased tumor size may not be visible on imaging for several weeks, mass-effect symptoms (eg, visual field defects) usually start to improve much sooner, often within the first several days of treatment **(Choices B and C)**, with eventual normalization in many cases.

Therefore, regardless of the adenoma size and severity of neurologic symptoms, dopamine agonists are the first-line therapy for prolactinoma. Surgery is not needed in most patients; even if surgery is performed, complete resection is often not possible, and recurrence is common, requiring medication therapy.

https://t.me/USMLEWorldStep1

imaging	• Tests to rule out renal insufficiency (creatinine) & hypothyroidism (TSH, thyroxine) • MRI of the head/pituitary
Treatment	• Dopamine agonist (cabergoline) • Transsphenoidal surgery

This patient has a prolactin-secreting pituitary adenoma (**prolactinoma**), confirmed with elevated serum prolactin and a pituitary mass visible on MRI. Prolactin can cause **hypogonadism** (eg, decreased libido, erectile dysfunction, gynecomastia) due to suppression of hypothalamic GnRH production. **Mass-effect symptoms** of the tumor commonly include headaches and visual field defects due to compression of the optic chiasm.

Unlike most pituitary hormones, which are under positive regulation by releasing hormones (eg, GnRH, TRH) from the hypothalamus, prolactin is primarily under negative regulation by dopaminergic neurons via the pituitary stalk. **Dopamine agonists** (eg, **cabergoline**, bromocriptine) are used in patients with prolactinomas to **suppress prolactin production** and **reduce tumor size**.

Prolactin levels typically fall significantly within the first **2-3 weeks** of therapy **(Choices D and E)**, with a corresponding improvement in hypogonadal symptoms. Although decreased tumor size may not be visible on imaging for several weeks, mass-effect symptoms (eg, visual field defects) usually start to improve much sooner, often within the first several days of treatment **(Choices B and C)**, with eventual normalization in many cases.

Therefore, regardless of the adenoma size and severity of neurologic symptoms, dopamine agonists are the first-line therapy for prolactinoma. Surgery is not needed in most patients; even if surgery is performed, complete resection is often not possible, and recurrence is common, requiring medication therapy.

Educational objective:
Prolactin is under negative regulation by dopaminergic neurons via the pituitary stalk. Dopamine agonists (eg, cabergoline) are used in patients with prolactin-secreting pituitary adenomas (prolactinomas) to suppress prolactin production and reduce tumor size. Benefits are typically seen within the first few weeks of therapy.

Pharmacology	Endocrine, Diabetes & Metabolism	Hyperprolactinemia
Subject	System	Topic

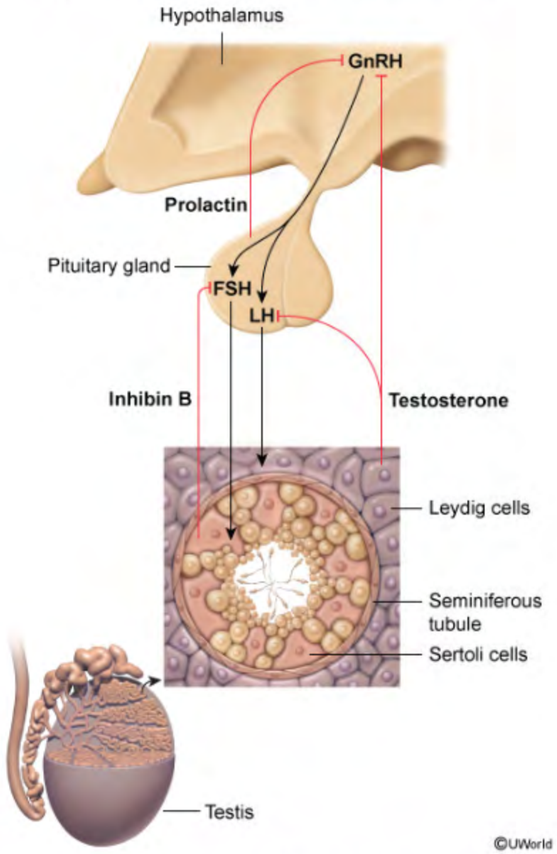
Copyright © UWorld. All rights reserved.

https://t.me/USMLEWorldStep1

imaging	• Tests to rule out renal insufficiency (creatinine) & hypothyroidism (TSH, thyroxine) • MRI of the head/pituitary

Exhibit Display

Prolactin and gonadotropin production



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

This p
and a
dysfun
tumor

Unlike
the hy
Dopar
prolac

Prolac
corres
imagin
often v

Theref
line th
resect

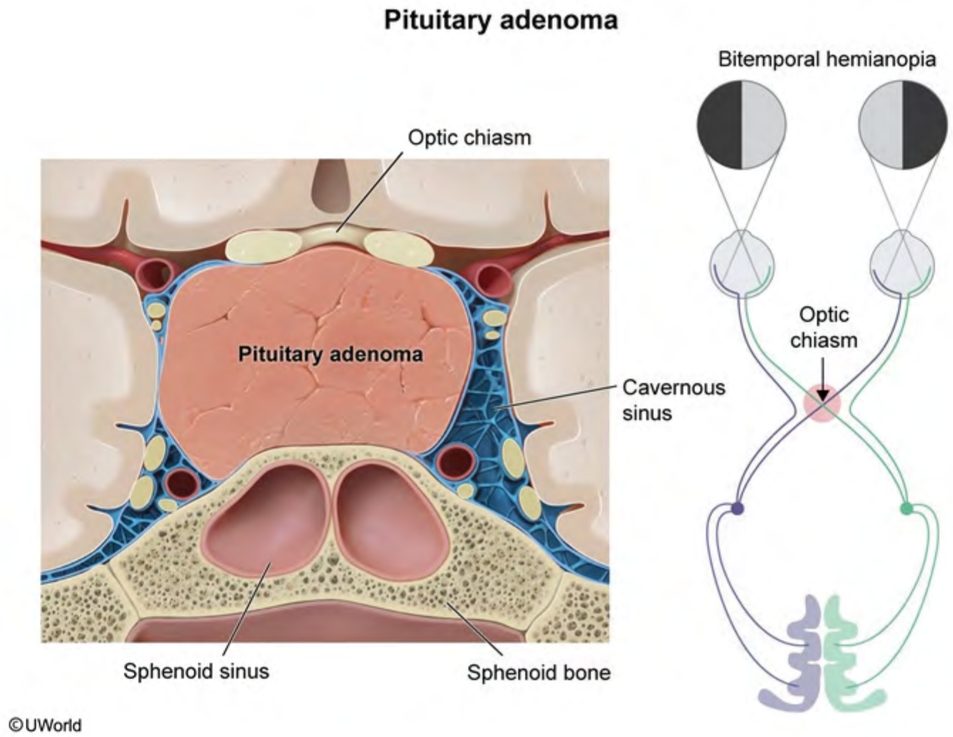
Educa
Prolac
caberg
produc

Pharma
Subject

Copyright © UWorld. All rights reserved.

imaging	• Tests to rule out renal insufficiency (creatinine) & hypothyroidism (TSH, thyroxine) • MRI of the head/pituitary

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

This p
and a
dysfur
tumor

Unlike
the hy
Dopar
prolac

Prolac
corres
imagir
often v

Theref
line th
resect

Educa
Prolac
caberg
produc

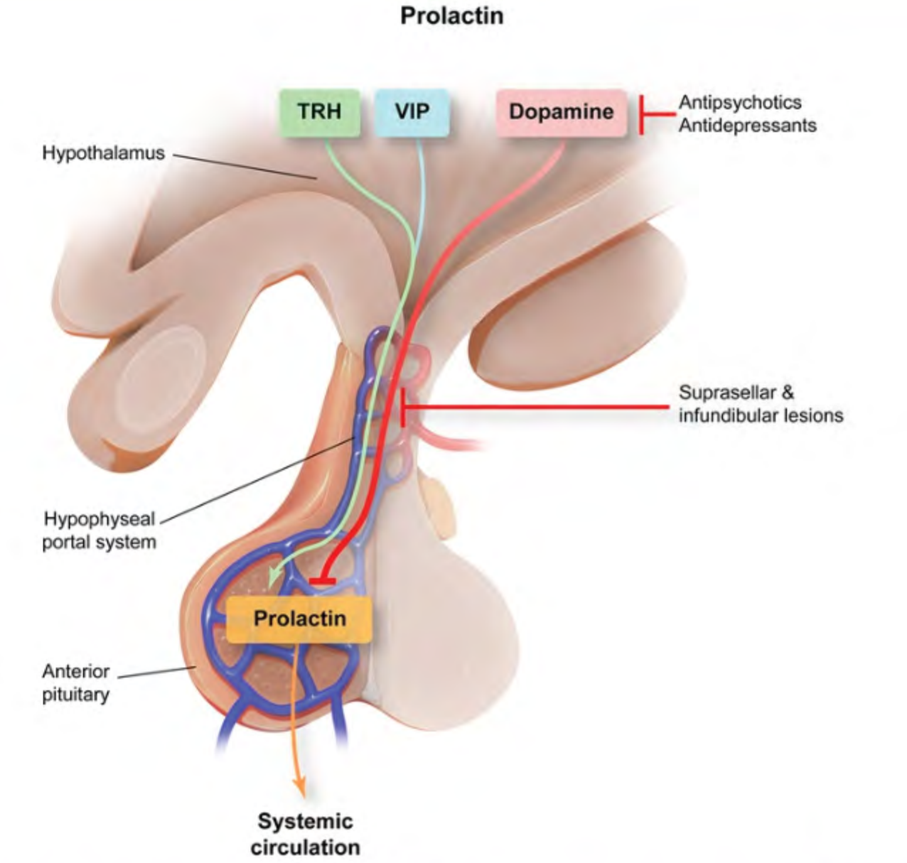
Pharma
Subject

Copyright © UWorld. All rights reserved.

https://t.me/USMLEWorldStep1

imaging	• Tests to rule out renal insufficiency (creatinine) & hypothyroidism (TSH, thyroxine) • MRI of the head/pituitary

Exhibit Display



TRH = thyrotropin-releasing hormone; VIP = vasoactive intestinal peptide.

©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

This p
and a
dysfur
tumor

Unlike
the hy
Dopar
prolac

Prolac
corres
imagir
often v

Theref
line th
resect

Educa
Prolac
caberg
produc

Pharma
Subject

Copyright © UWorld. All rights reserved.

https://t.me/USMLEWorldStep1

A 28-year-old woman, gravida 1 para 1, comes to the office for a follow-up appointment 4 months after giving birth to a healthy boy. For the past 3 weeks the patient has had progressive fatigue associated with loss of interest in day-to-day activities, irritability, and poor concentration. In the 2 weeks prior to the onset of fatigue, she experienced excessive sweating and palpitations. Blood pressure is 140/74 mm Hg and pulse is 60/min. The thyroid gland is firm, diffusely enlarged, and nontender. Laboratory results show elevated serum TSH and low free T4. Which of the following pathological processes is likely responsible for this patient's condition?

- A. Dense fibrous replacement of the thyroid gland
- B. Granulomatous inflammation of the pituitary hypophysis
- C. Granulomatous inflammation of the thyroid gland
- D. Lymphocyte-mediated thyroid follicular damage
- E. Lymphocytic infiltration of the pituitary hypophysis

Submit

https://t.me/USMLEWorldStep1

A 28-year-old woman, gravida 1 para 1, comes to the office for a follow-up appointment 4 months after giving birth to a healthy boy. For the past 3 weeks the patient has had progressive fatigue associated with loss of interest in day-to-day activities, irritability, and poor concentration. In the 2 weeks prior to the onset of fatigue, she experienced excessive sweating and palpitations. Blood pressure is 140/74 mm Hg and pulse is 60/min. The thyroid gland is firm, diffusely enlarged, and nontender. Laboratory results show elevated serum TSH and low free T4. Which of the following pathological processes is likely responsible for this patient's condition?

- A. Dense fibrous replacement of the thyroid gland (8%)
- ✗ B. Granulomatous inflammation of the pituitary hypophysis (2%)
- C. Granulomatous inflammation of the thyroid gland (15%)
- ✓ D. Lymphocyte-mediated thyroid follicular damage (69%)
- E. Lymphocytic infiltration of the pituitary hypophysis (4%)

Incorrect
Correct answer
D

69%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

Postpartum thyroiditis	
Pathophysiology	• Autoimmune destruction of thyroid follicles & release of preformed thyroid hormone • Lymphocytic infiltrates ± germinal centers
Clinical course	• Onset ≤12 months after pregnancy • Transient hyperthyroid phase (↑ T4 & T3, ↓ TSH) • Brief hypothyroid phase (↓ T4 & T3, ↑ TSH) • Return to euthyroid state

https://t.me/USMLEWorldStep1

Postpartum thyroiditis	
Pathophysiology	• Autoimmune destruction of thyroid follicles & release of preformed thyroid hormone • Lymphocytic infiltrates ± germinal centers
Clinical course	• Onset ≤12 months after pregnancy • Transient hyperthyroid phase (↑ T4 & T3, ↓ TSH) • Brief hypothyroid phase (↓ T4 & T3, ↑ TSH) • Return to euthyroid state
Diagnosis	• ↑ Serum thyroglobulin • ↓ Radioiodine uptake • Ultrasound: diffuse thyroid enlargement with ↓ blood flow
T3 = triiodothyronine; **T4** = thyroxine.	

This patient has primary hypothyroidism, presenting with a low serum thyroxine level and elevated TSH, associated with fatigue and neurocognitive symptoms. Immediately preceding this, she had symptoms suggesting hyperthyroidism (ie, palpitation, diaphoresis). In light of her recent childbirth, this phasic pattern of thyroid dysfunction is most consistent with postpartum thyroiditis.

Postpartum thyroiditis occurs within 12 months of pregnancy and is characterized by **autoimmune destruction of thyroid follicles** similar to that seen in chronic lymphocytic (Hashimoto) thyroiditis. It typically begins with a hyperthyroid phase due to **release of preformed thyroid hormone**, followed by a transient hypothyroid phase due to depletion of thyroid hormone and an eventual return to a euthyroid state.

Postpartum thyroiditis is associated with high titers of **antithyroid peroxidase and antithyroglobulin autoantibodies**, which activate complement in thyroid follicles and stimulate NK cells. Histologic inspection demonstrates **lymphocytic infiltration**, sometimes with formation of germinal centers. Breakdown of follicle margins and loss of colloid may also be seen.

(Choice A) Riedel thyroiditis is a rare disorder characterized by extensive fibrosis of the thyroid that extends into surrounding tissues. The thyroid gland is hard and fixed. Hypothyroidism is common but is not typically preceded

https://t.me/USMLEWorldStep1

dysfunction is most consistent with postpartum thyroiditis.

Postpartum thyroiditis occurs within 12 months of pregnancy and is characterized by **autoimmune destruction of thyroid follicles** similar to that seen in chronic lymphocytic (Hashimoto) thyroiditis. It typically begins with a hyperthyroid phase due to **release of preformed thyroid hormone**, followed by a transient hypothyroid phase due to depletion of thyroid hormone and an eventual return to a euthyroid state.

Postpartum thyroiditis is associated with high titers of **antithyroid peroxidase and antithyroglobulin autoantibodies**, which activate complement in thyroid follicles and stimulate NK cells. Histologic inspection demonstrates **lymphocytic infiltration**, sometimes with formation of germinal centers. Breakdown of follicle margins and loss of colloid may also be seen.

(Choice A) Riedel thyroiditis is a rare disorder characterized by extensive fibrosis of the thyroid that extends into surrounding tissues. The thyroid gland is hard and fixed. Hypothyroidism is common but is not typically preceded by a hyperthyroid phase.

(Choices B and E) Granulomatous inflammation in the pituitary can occur as a primary phenomenon or secondary to systemic granulomatous disorders (eg, sarcoidosis, tuberculosis). Lymphocytic hypophysitis is an uncommon disorder that also occurs with increased frequency in postpartum women. Both of these disorders can cause secondary/central hypothyroidism due to loss of pituitary thyrotrophs, which leads to low (not elevated) TSH.

(Choice C) Like postpartum thyroiditis, subacute (postviral, granulomatous, De Quervain) thyroiditis also follows a phasic course with initial hyperthyroidism due to release of preformed hormone followed by a hypothyroid phase. However, the thyroid is painful and tender, and fever is common because it is believed to be a postviral inflammatory process.

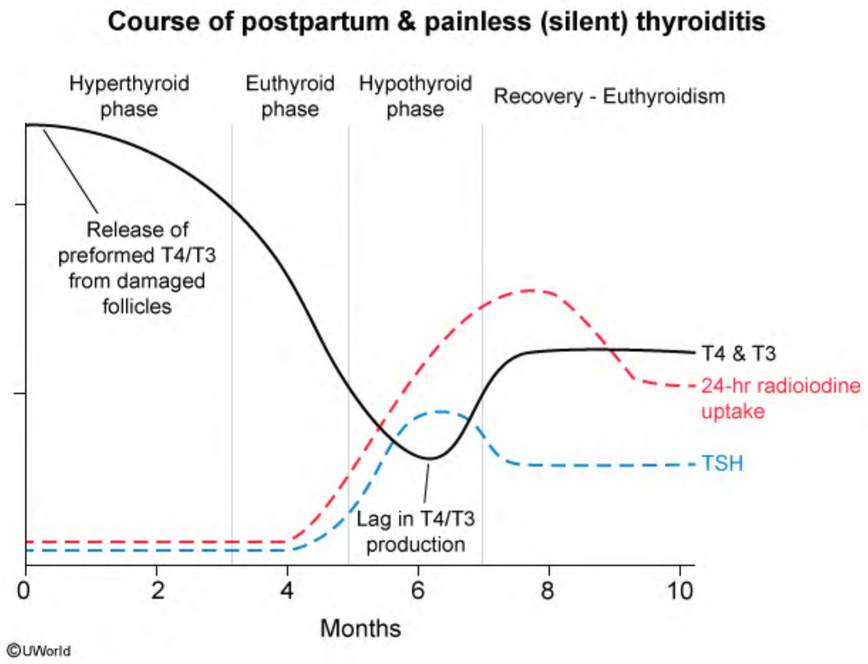
Educational objective:
Postpartum thyroiditis occurs within 12 months of pregnancy and is characterized by autoimmune destruction of thyroid follicles. It begins with a hyperthyroid phase due to release of preformed thyroid hormone, followed by a transient hypothyroid phase due to depletion of thyroid hormone. Histologic inspection demonstrates lymphocytic infiltration, sometimes with formation of germinal centers.

Pathology Endocrine, Diabetes & Metabolism Hypothyroidism

https://t.me/USMLEWorldStep1

Diagnosis	• ↓ Radioiodine uptake • Ultrasound: diffuse thyroid enlargement with ↓ blood flow

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

This p
with fa
hypert
dysfun

Postp
of thy
hypert
to dep

Postpa
autoa
demor
margi

(Choi
surrou
by a h

(Choi
secon
uncom
cause

(Choi
phasic
Howev
inflammatory process.

https://t.me/USMLEWorldStep1

Diagnosis	• ↓ Radioiodine uptake • Ultrasound: diffuse thyroid enlargement with ↓ blood flow

Exhibit Display

Differential diagnosis of thyroiditis

Painful thyroiditis Pain & tenderness Systemic symptoms	**Painless thyroiditis** Autoimmune/+TPO antibody Destruction of follicles Release of preformed hormone & thyroglobulin	**Graves** +TSI/TRAb ↑ Thyroid hormone synthesis	**Fibrotic** Replacement of follicles with fibrotic tissue
Subacute (granulomatous, DeQuervain) • Tender goiter • Transient hyperthyroid phase • Postviral syndrome **Acute** (suppurative) • Fever • Asymmetry • Fluctuance	**Chronic lymphocytic** (Hashimoto) • Common • Usually hypothyroid at diagnosis **Postpartum** • ≤12 months after parturition • Transient hyperthyroid phase	**Graves disease** • Overt hyperthyroidism • ↑ RAIU • Ophthalmopathy	**Riedel thyroiditis** • Hard/fixed goiter • Compression of esophagus & trachea

TPO = thyroid peroxidase; **TSI** = thyroid-stimulating immunoglobulin; **TRAb** = thyrotropin receptor antibody; **RAIU** = radioiodine uptake.

©UWorld

Zoom In Zoom Out Reset New | Existing My Notebook

This p
with fa
hypert
dysfun

Postp
of thy
hypert
to dep

Postpa
autoa
demor
margi

(Choi
surrou
by a h

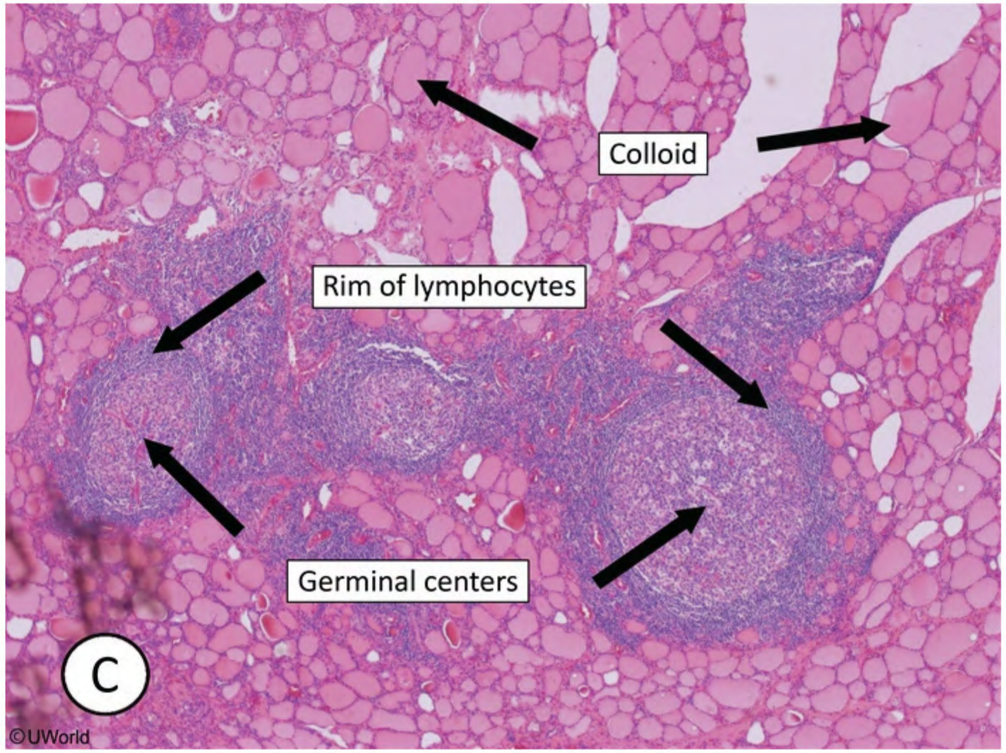
(Choi
secon
uncom
cause

(Choi
phasic
Howev
inflammatory process.

https://t.me/USMLEWorldStep1

Diagnosis	• ↓ Radioiodine uptake • Ultrasound: diffuse thyroid enlargement with ↓ blood flow

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

This p
with fa
hypert
dysfur

Postp
of thy
hypert
to dep

Postpa
autoa
demor
margir

(Choi
surrou
by a h

(Choi
secon
uncom
cause

(Choi
phasic
Howev
inflammatory process.

https://t.me/USMLEWorldStep1

A 50-year-old woman enrolls in a clinical trial testing a medication for type 2 diabetes mellitus that may slow the progression of or reverse nonalcoholic steatohepatitis (NASH). Medical history includes type 2 diabetes mellitus and NASH, which was diagnosed a year ago by biopsy. Medications include metformin, atorvastatin, and aspirin. Laboratory studies show a fasting glucose of 155 mg/dL, hemoglobin A1c of 8.2%, ALT of 85 U/L, and AST of 74 U/L. The study drug will be taken in addition to metformin to enhance glycemic control, and markers for NASH-related disease activity will be measured at 12 months. The study drug activates peroxisome proliferator–activated receptor gamma, a nuclear receptor and transcription factor. Activation of this receptor would most likely result in which of the following metabolic changes?

- A. Decreased insulin resistance
- B. Downregulation of adiponectin
- C. Increased free fatty acid levels
- D. Increased insulin release
- E. Upregulation of leptin activity

Submit

https://t.me/USMLEWorldStep1

A 50-year-old woman enrolls in a clinical trial testing a medication for type 2 diabetes mellitus that may slow the progression of or reverse nonalcoholic steatohepatitis (NASH). Medical history includes type 2 diabetes mellitus and NASH, which was diagnosed a year ago by biopsy. Medications include metformin, atorvastatin, and aspirin. Laboratory studies show a fasting glucose of 155 mg/dL, hemoglobin A1c of 8.2%, ALT of 85 U/L, and AST of 74 U/L. The study drug will be taken in addition to metformin to enhance glycemic control, and markers for NASH-related disease activity will be measured at 12 months. The study drug activates peroxisome proliferator–activated receptor gamma, a nuclear receptor and transcription factor. Activation of this receptor would most likely result in which of the following metabolic changes?

- ✓ A. Decreased insulin resistance (49%)
- ✗ B. Downregulation of adiponectin (13%)
- C. Increased free fatty acid levels (12%)
- D. Increased insulin release (16%)
- E. Upregulation of leptin activity (7%)

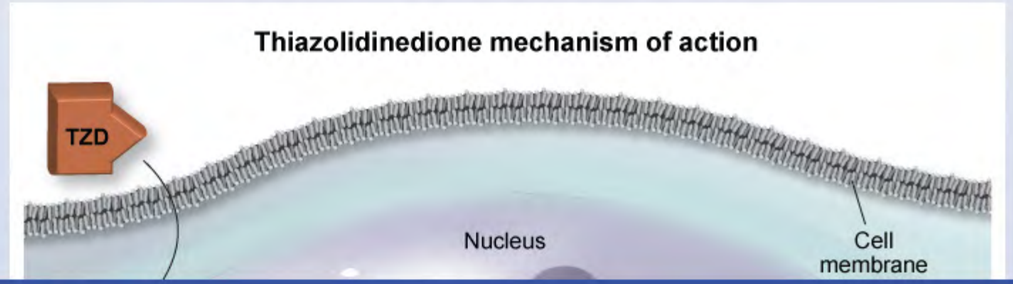
Incorrect
Correct answer
A

49%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

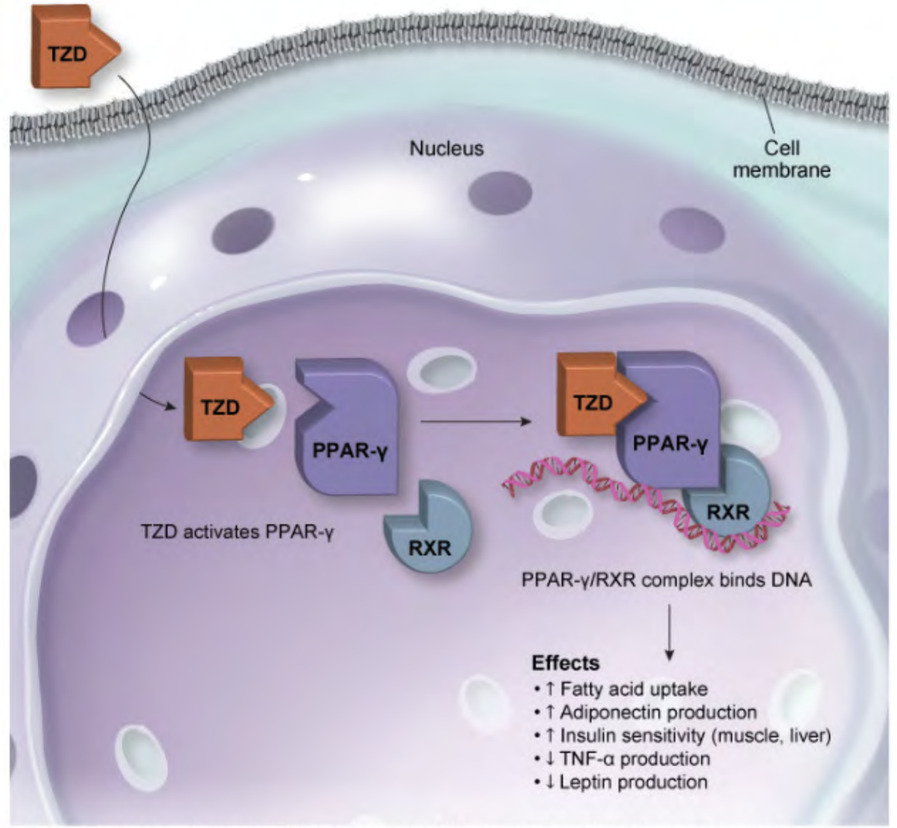


https://t.me/USMLEWorldStep1

A 50-year-old woman enrolls in a clinical trial testing a medication for type 2 diabetes mellitus that may slow the progre
and N
Labora
U/L. T
related
recept
which

Exhibit Display

Thiazolidinedione mechanism of action



PPAR-γ = peroxisome proliferator–activated receptor gamma; **RXR** = retinoid X receptor; **TZD** = thiazolidinedione. ©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Nucleus
Cell membrane

https://t.me/USMLEWorldStep1



PPAR-γ = peroxisome proliferator–activated receptor gamma; **RXR** = retinoid X receptor; **TZD** = thiazolidinedione. ©UWorld

This clinical trial is studying a **thiazolidinedione** (TZD), a class of medications that **decrease insulin resistance**, a key pathologic factor in both type 2 diabetes mellitus and nonalcoholic steatohepatitis (NASH).

TZDs (eg, pioglitazone) bind to **peroxisome proliferator–activated receptor gamma** (PPAR-γ), a transcriptional regulator of genes involved in glucose and lipid metabolism. The activated complex then binds to the transcriptional regulatory sequences to upregulate target genes that enhance insulin sensitivity, including:

- **Glucose transporter-4**, an insulin-responsive, transmembrane glucose transporter expressed in adipocytes and skeletal myocytes that increases glucose uptake by target cells
- **Adiponectin**, a cytokine secreted by fat tissue that increases the number of insulin-responsive adipocytes and stimulates fatty acid oxidation **(Choice B)**

TZDs are functionally similar to fibrate medications (eg, fenofibrate, gemfibrozil), which bind PPAR-α and are effective in lowering blood triglyceride levels. The PPAR family of transcriptional regulators also plays a significant role in the pathogenesis of metabolic syndrome (obesity, hypertension, dyslipidemia, and insulin resistance), and their activation and subsequent increase in insulin sensitivity are thought to reverse the histologic changes in NASH.

(Choice C) PPAR-γ activation leads to an increase in fat mass secondary to the increased differentiation of preadipocytes into mature adipocytes. The increased movement of free fatty acids into fat cells, along with increased fatty acid oxidation (adiponectin effect), causes circulating free fatty acid levels to decrease.

(Choice D) TZDs do not stimulate insulin secretion; rather, as insulin resistance diminishes, circulating levels of insulin tend to decrease over time.

(Choice E) Leptin is a hormone secreted by fat cells that acts on the hypothalamus to decrease appetite. Although PPAR-γ activation increases fat cell mass, circulating leptin levels remain unchanged or decrease due to the inhibiting effect of PPAR-γ on leptin gene transcription.

Educational objective:

https://t.me/USMLEWorldStep1

This clinical trial is studying a **thiazolidinedione** (TZD), a class of medications that **decrease insulin resistance**, a key pathologic factor in both type 2 diabetes mellitus and nonalcoholic steatohepatitis (NASH).

TZDs (eg, pioglitazone) bind to **peroxisome proliferator–activated receptor gamma** (PPAR-γ), a transcriptional regulator of genes involved in glucose and lipid metabolism. The activated complex then binds to the transcriptional regulatory sequences to upregulate target genes that enhance insulin sensitivity, including:

- **Glucose transporter-4**, an insulin-responsive, transmembrane glucose transporter expressed in adipocytes and skeletal myocytes that increases glucose uptake by target cells
- **Adiponectin**, a cytokine secreted by fat tissue that increases the number of insulin-responsive adipocytes and stimulates fatty acid oxidation **(Choice B)**

TZDs are functionally similar to fibrate medications (eg, fenofibrate, gemfibrozil), which bind PPAR-α and are effective in lowering blood triglyceride levels. The PPAR family of transcriptional regulators also plays a significant role in the pathogenesis of metabolic syndrome (obesity, hypertension, dyslipidemia, and insulin resistance), and their activation and subsequent increase in insulin sensitivity are thought to reverse the histologic changes in NASH.

(Choice C) PPAR-γ activation leads to an increase in fat mass secondary to the increased differentiation of preadipocytes into mature adipocytes. The increased movement of free fatty acids into fat cells, along with increased fatty acid oxidation (adiponectin effect), causes circulating free fatty acid levels to decrease.

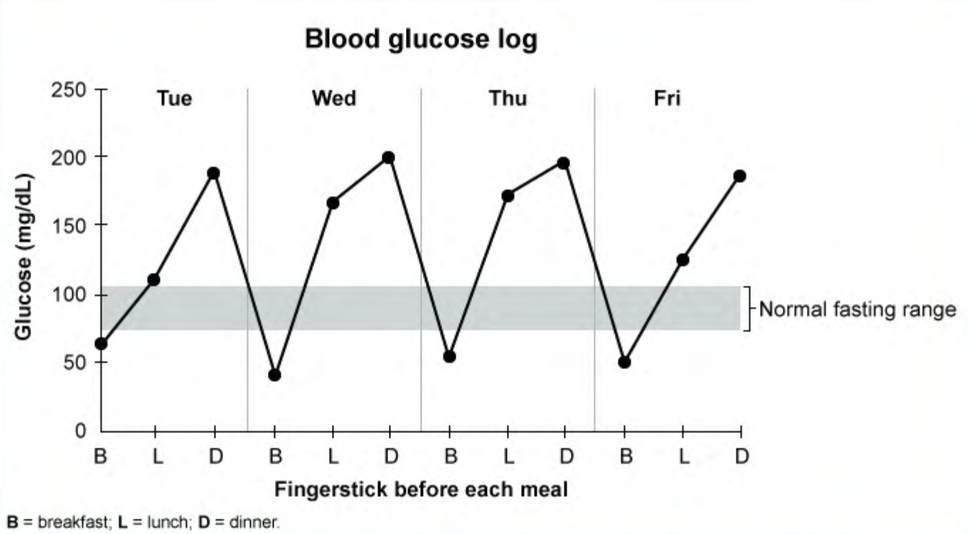
(Choice D) TZDs do not stimulate insulin secretion; rather, as insulin resistance diminishes, circulating levels of insulin tend to decrease over time.

(Choice E) Leptin is a hormone secreted by fat cells that acts on the hypothalamus to decrease appetite. Although PPAR-γ activation increases fat cell mass, circulating leptin levels remain unchanged or decrease due to the inhibiting effect of PPAR-γ on leptin gene transcription.

Educational objective:
Thiazolidinediones (TZDs) activate peroxisome proliferator–activated receptor gamma, a nuclear receptor that alters the transcription of genes involved in glucose and lipid metabolism. The resulting decrease in insulin resistance lowers blood glucose and can help reverse nonalcoholic steatohepatitis.

https://t.me/USMLEWorldStep1

A 19-year-old woman with cystic fibrosis comes to the clinic due to episodes of nausea, lightheadedness, and diaphoresis. The episodes started 3 months ago. She feels better after eating a candy bar. The patient has also experienced polyuria and a 4.5-kg (10-lb) weight loss. Current medications include pancreatic enzyme supplements and nebulized respiratory treatments. BMI is 19.5 kg/m^2. Physical examination is unremarkable. Glucose level measured by random fingerstick check is elevated at 201 mg/dL, and hemoglobin A1c is 6.8%. The patient is asked to measure and record her blood glucose level prior to each meal. The results over 4 days are shown below.



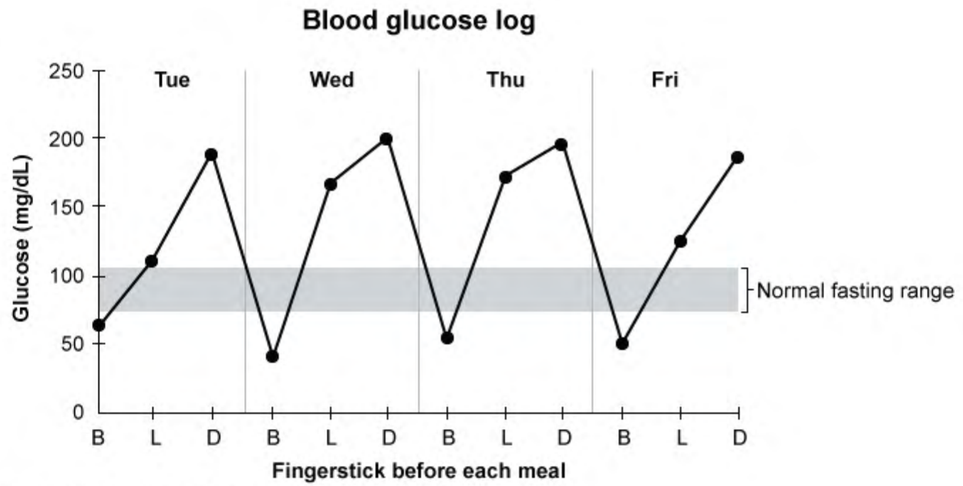
Which of the following is most likely responsible for this patient's low blood glucose levels?

A. Decreased insulin clearance
B. Ectopic insulin secretion
C. Impaired glucagon release
D. Increased trypsinogen excretion
E. Reduced cortisol production

https://t.me/USMLEWorldStep1

A 19-year-old woman with cystic fibrosis comes to the clinic due to episodes of nausea, lightheadedness, and diapho
experi
supple
Glucos
patien
shown

Exhibit Display



B = breakfast; **L** = lunch; **D** = dinner.

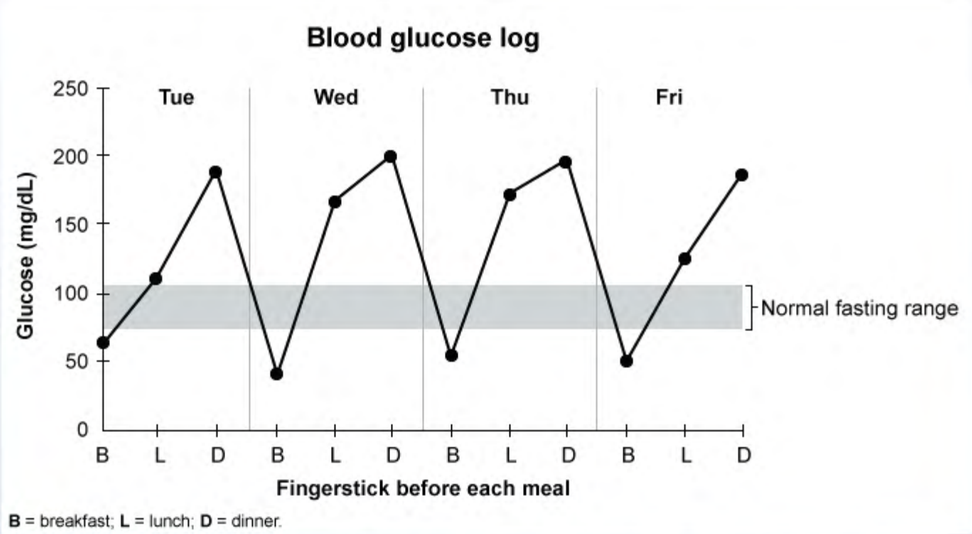
Zoom In Zoom Out Reset New | Existing My Notebook

Which

D. Increased trypsinogen excretion
E. Reduced cortisol production

https://t.me/USMLEWorldStep1

supplements and nebulized respiratory treatments. BMI is 19.5 kg/m^2. Physical examination is unremarkable. Glucose level measured by random fingerstick check is elevated at 201 mg/dL, and hemoglobin A1c is 6.8%. The patient is asked to measure and record her blood glucose level prior to each meal. The results over 4 days are shown below.



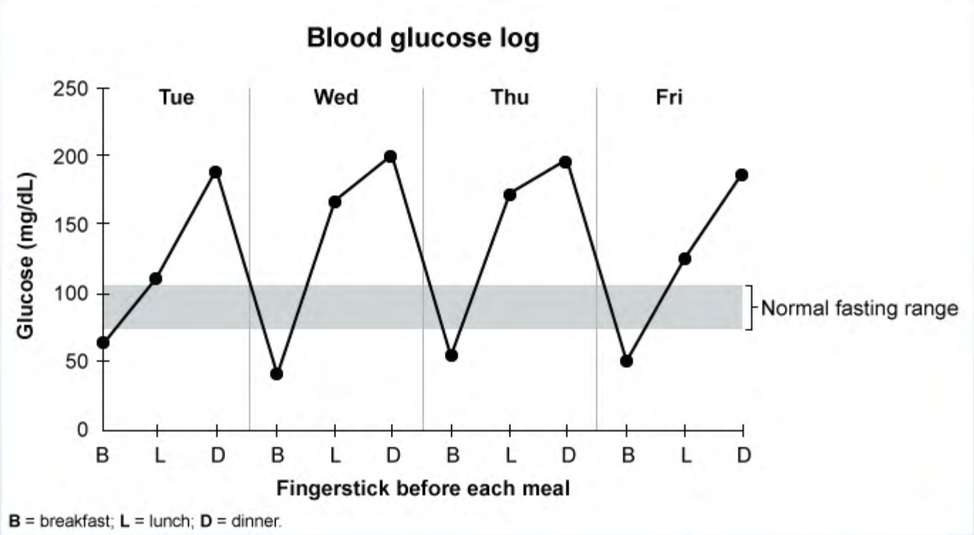
Which of the following is most likely responsible for this patient's low blood glucose levels?

- A. Decreased insulin clearance
- B. Ectopic insulin secretion
- C. Impaired glucagon release
- D. Increased trypsinogen excretion
- E. Reduced cortisol production

Submit

https://t.me/USMLEWorldStep1

supplements and nebulized respiratory treatments. BMI is 19.5 kg/m². Physical examination is unremarkable. Glucose level measured by random fingerstick check is elevated at 201 mg/dL, and hemoglobin A1c is 6.8%. The patient is asked to measure and record her blood glucose level prior to each meal. The results over 4 days are shown below.



Which of the following is most likely responsible for this patient's low blood glucose levels?

- A. Decreased insulin clearance (14%)
- ✗ B. Ectopic insulin secretion (8%)
- ✓ C. Impaired glucagon release (61%)
- D. Increased trypsinogen excretion (5%)
- E. Reduced cortisol production (10%)

Incorrect
Correct answer
C

61%
Answered correctly

11 secs
Time Spent

2023
Version

https://t.me/USMLEWorldStep1

Explanation

This patient with cystic fibrosis (CF) exhibits glucose dysregulation, suggesting clinical onset of endocrine pancreatic failure. In patients with CF, ductal obstruction by thickened secretions leads to exocrine pancreatic insufficiency (eg, fat malabsorption) early in life. Buildup of pancreatic enzymes also results in pancreatic autolysis, chronic inflammation, and fibrosis, with progressive destruction of the endocrine pancreas. Eventually, a form of **pancreatogenic diabetes** mellitus, referred to as CF-related diabetes (CFRD), can develop.

Nonselective loss of alpha and beta pancreatic islet cells explains this patient's glucose fluctuations.

- Loss of **alpha cells** leads to **glucagon deficiency**. Glucagon is the primary counterregulatory hormone. It stimulates glycogenolysis and gluconeogenesis to defend against hypoglycemia in the fasting state (eg, prior to breakfast). Because alpha cells make up only 20% of islet mass, absolute glucagon deficiency occurs earlier in the course of CFRD, often preceding absolute insulin deficiency.
- Loss of beta cells leads to insulin deficiency, contributing to hyperglycemia and catabolic symptoms (eg, weight loss). This patient's postprandial hyperglycemia indicates failure of the beta-cell response to dietary carbohydrate intake.

This **early loss of glucagon** accounts for more frequent episodes of **hypoglycemia** compared to patients with non-pancreatogenic (eg, type 2) diabetes mellitus. A similar phenomenon also affects patients following pancreas resection (eg, Whipple procedure).

(Choice A) Decreased insulin clearance causes hypoglycemia in patients with renal insufficiency who are receiving exogenous insulin therapy.

(Choice B) Ectopic insulin secretion (eg, insulinoma) can cause fasting and paroxysmal hypoglycemia but would not explain this patient's hyperglycemia, polyuria (osmotic diuresis), or weight loss, which are signs of insulin deficiency, rather than excess.

(Choice D) Decreased (rather than increased) pancreatic trypsinogen production contributes to dietary protein malabsorption and low skeletal muscle mass in patients with CF (eg, this patient's sarcopenia and low BMI).

(Choice E) Decreased cortisol production (eg, primary adrenal insufficiency) can precipitate hypoglycemia,

https://t.me/USMLEWorldStep1

form of **pancreatogenic diabetes** mellitus, referred to as CF-related diabetes (CFRD), can develop.

Nonselective loss of alpha and beta pancreatic islet cells explains this patient's glucose fluctuations.

- Loss of **alpha cells** leads to **glucagon deficiency**. Glucagon is the primary counterregulatory hormone. It stimulates glycogenolysis and gluconeogenesis to defend against hypoglycemia in the fasting state (eg, prior to breakfast). Because alpha cells make up only 20% of islet mass, absolute glucagon deficiency occurs earlier in the course of CFRD, often preceding absolute insulin deficiency.
- Loss of beta cells leads to insulin deficiency, contributing to hyperglycemia and catabolic symptoms (eg, weight loss). This patient's postprandial hyperglycemia indicates failure of the beta-cell response to dietary carbohydrate intake.

This **early loss of glucagon** accounts for more frequent episodes of **hypoglycemia** compared to patients with non-pancreatogenic (eg, type 2) diabetes mellitus. A similar phenomenon also affects patients following pancreas resection (eg, Whipple procedure).

(Choice A) Decreased insulin clearance causes hypoglycemia in patients with renal insufficiency who are receiving exogenous insulin therapy.

(Choice B) Ectopic insulin secretion (eg, insulinoma) can cause fasting and paroxysmal hypoglycemia but would not explain this patient's hyperglycemia, polyuria (osmotic diuresis), or weight loss, which are signs of insulin deficiency, rather than excess.

(Choice D) Decreased (rather than increased) pancreatic trypsinogen production contributes to dietary protein malabsorption and low skeletal muscle mass in patients with CF (eg, this patient's sarcopenia and low BMI).

(Choice E) Decreased cortisol production (eg, primary adrenal insufficiency) can precipitate hypoglycemia, especially in the setting of physiologic stress (eg, infection). However, adrenal steroid synthesis is unaffected by CF, and cortisol deficiency would not explain the patient's hyperglycemia.

Educational objective:
Pancreatic disease in cystic fibrosis is characterized by nonselective destruction of alpha and beta cells. Because alpha cells make up the minority of islet mass, glucagon deficiency and fasting hypoglycemia occur early in the diabetic disease course.

https://t.me/USMLEWorldStep1

Explanation

This p
pancre
insuffi
autoly
form o

Nonse

- L
st
to
e
- L
w
c

This **e**
non-pa
resect

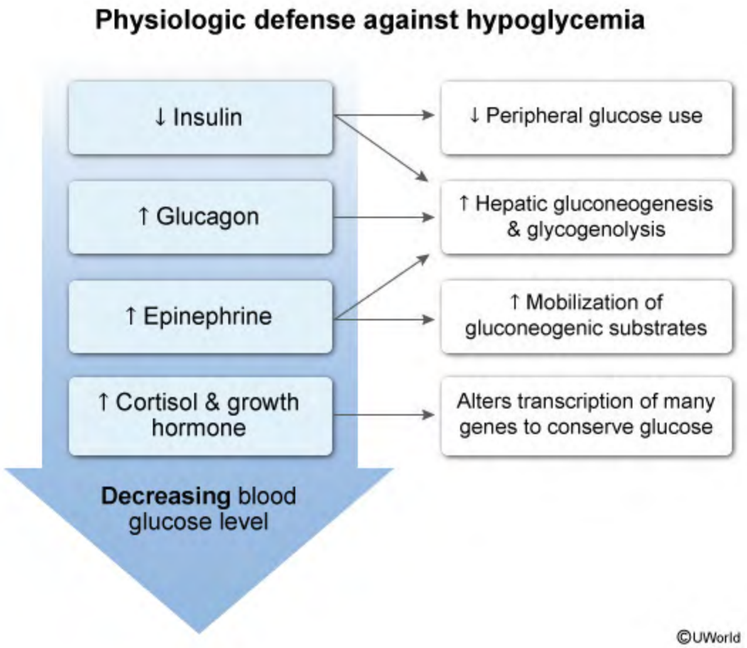
(Choi
receivi

(Choi
not ex
deficie

(Choi
malabsorption and low skeletal muscle mass in patients with CF (eg, this patient's sarcopenia and low BMI).

(Choice E) Decreased cortisol production (eg, primary adrenal insufficiency) can precipitate hypoglycemia,

Exhibit Display



Zoom In Zoom Out Reset New | Existing My Notebook

https://t.me/USMLEWorldStep1

Explanation

This p
pancre
insuffi
autoly
form o

Nonse

- L
st
to
e
- L
w
c

This **e**
non-pa
resect

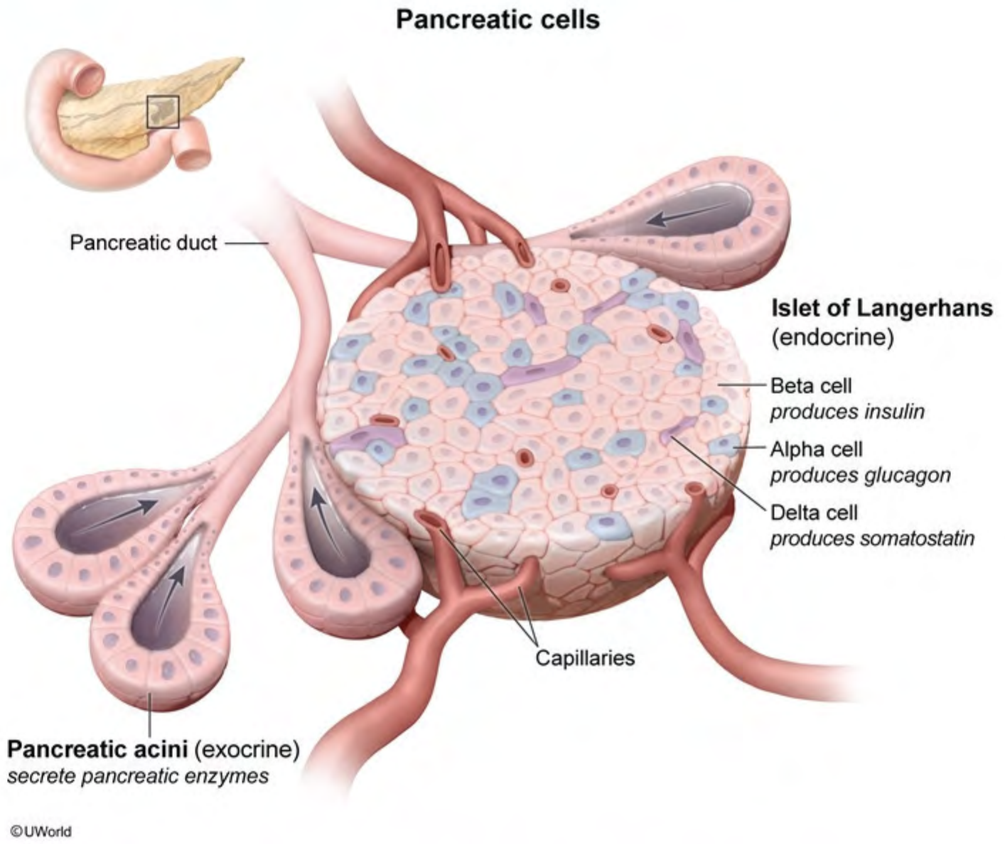
(Choi
receivi

(Choi
not ex
deficie

(Choi
malabsorption and low skeletal muscle mass in patients with CF (eg, this patient's sarcopenia and low BMI).

(Choice E) Decreased cortisol production (eg, primary adrenal insufficiency) can precipitate hypoglycemia,

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

A 34-year-old woman comes to the office due to a 1 week history of mood swings, difficulty concentrating, and hand tremors. She also has pain at the front of her neck that radiates to her ears and is worse with swallowing. The patient initially attributed her symptoms to a flu-like illness that she had a few weeks earlier. She has no other medical conditions and takes no medications. Blood pressure is 140/80 mm Hg and pulse is 105/min. The thyroid gland is very tender on palpation. After initial laboratory testing, a thyroid scan is performed and reveals diffusely decreased radioiodine uptake. Erythrocyte sedimentation rate is 105 mm/hr. Which of the following pathological changes would most likely be found on biopsy of this patient's thyroid gland?

- A. Branching papillary structures with interspersed calcified bodies
- B. Extensive stromal fibrosis extending beyond the thyroid capsule
- C. Follicular hyperplasia with tall cells forming intrafollicular papillary projections
- D. Mixed cellular infiltration with occasional multinucleated giant cells
- E. Mononuclear infiltration with well-developed germinal centers

Submit

https://t.me/USMLEWorldStep1

A 34-year-old woman comes to the office due to a 1 week history of mood swings, difficulty concentrating, and hand tremors. She also has pain at the front of her neck that radiates to her ears and is worse with swallowing. The patient initially attributed her symptoms to a flu-like illness that she had a few weeks earlier. She has no other medical conditions and takes no medications. Blood pressure is 140/80 mm Hg and pulse is 105/min. The thyroid gland is very tender on palpation. After initial laboratory testing, a thyroid scan is performed and reveals diffusely decreased radioiodine uptake. Erythrocyte sedimentation rate is 105 mm/hr. Which of the following pathological changes would most likely be found on biopsy of this patient's thyroid gland?

- ✗ A. Branching papillary structures with interspersed calcified bodies (3%)
- B. Extensive stromal fibrosis extending beyond the thyroid capsule (7%)
- C. Follicular hyperplasia with tall cells forming intrafollicular papillary projections (9%)
- ✓ D. Mixed cellular infiltration with occasional multinucleated giant cells (55%)
- E. Mononuclear infiltration with well-developed germinal centers (24%)

Incorrect
Correct answer
D

55%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

Important causes of thyroiditis		
	Subacute granulomatous thyroiditis	**Hashimoto thyroiditis**
Clinical features	• Onset following a **viral illness** • **Painful** thyroid enlargement • Transient **hyperthyroid** symptoms	• **Autoimmune** etiology • **Painless** thyroid enlargement • Predominant **hypothyroid** features
Diagnostic	• ↑ ESR & CRP	• Positive **TPO antibody**

https://t.me/USMLEWorldStep1

Important causes of thyroiditis		
	Subacute granulomatous thyroiditis	**Hashimoto thyroiditis**
Clinical features	• Onset following a **viral illness** • **Painful** thyroid enlargement • Transient **hyperthyroid** symptoms	• **Autoimmune** etiology • **Painless** thyroid enlargement • Predominant **hypothyroid** features
Diagnostic testing	• ↑ ESR & CRP • ↓ Radioiodine uptake	• Positive **TPO antibody** • Variable radioiodine uptake
Pathology	• Inflammatory infiltrate with macrophages & **giant cells**	• Lymphocytic infiltrate with well-developed **germinal centers** • **Hürthle cells** (eosinophilic epithelial cells)
CRP = C-reactive protein; **ESR** = erythrocyte sedimentation rate; **TPO** = thyroid peroxidase.		

This patient with **painful** enlargement of the thyroid gland has **subacute granulomatous thyroiditis** (SGT), also called de Quervain thyroiditis. SGT typically follows an acute **viral illness** and is thought to be due to a cross-reacting immune response against viral proteins or tissue antigens released during cellular injury. Patients may experience a **transient hyperthyroid phase** (elevated thyroxine [T4], suppressed TSH) due to release of stored thyroid hormone. Radioiodine uptake is decreased in SGT as the low TSH levels suppress synthesis of new thyroid hormone. The disease is self-limited and resolves in <6 weeks.

SGT is initially characterized by a neutrophilic infiltrate with microabscess formation, which, as the disease progresses, is replaced by a more generalized inflammatory infiltrate with macrophages and **multinucleated giant cells**. The inflammatory process is reflected by elevated serum acute-phase markers (eg, C-reactive protein, erythrocyte sedimentation rate).

(Choice A) Papillary thyroid cancer is characterized by branching papillary structures with concentric calcifications (psammoma bodies). This malignancy would typically present with nodular enlargement rather than acute pain and tenderness.

https://t.me/USMLEWorldStep1

CRP = C-reactive protein; **ESR** = erythrocyte sedimentation rate; **TPO** = thyroid peroxidase.

This patient with **painful** enlargement of the thyroid gland has **subacute granulomatous thyroiditis** (SGT), also called de Quervain thyroiditis. SGT typically follows an acute **viral illness** and is thought to be due to a cross-reacting immune response against viral proteins or tissue antigens released during cellular injury. Patients may experience a **transient hyperthyroid phase** (elevated thyroxine [T4], suppressed TSH) due to release of stored thyroid hormone. Radioiodine uptake is decreased in SGT as the low TSH levels suppress synthesis of new thyroid hormone. The disease is self-limited and resolves in <6 weeks.

SGT is initially characterized by a neutrophilic infiltrate with microabscess formation, which, as the disease progresses, is replaced by a more generalized inflammatory infiltrate with macrophages and **multinucleated giant cells**. The inflammatory process is reflected by elevated serum acute-phase markers (eg, C-reactive protein, erythrocyte sedimentation rate).

(Choice A) Papillary thyroid cancer is characterized by branching papillary structures with concentric calcifications (psammoma bodies). This malignancy would typically present with nodular enlargement rather than acute pain and tenderness.

(Choice B) Riedel thyroiditis is characterized by extensive fibrosis of the thyroid gland that extends into surrounding tissues. The thyroid gland is hard and nontender.

(Choice C) Diffusely hyperplastic follicles with tall, crowded cells forming intrafollicular projections can be seen in Graves disease, which would show increased radioiodine uptake due to excessive TSH receptor stimulation.

(Choice E) Chronic lymphocytic (Hashimoto) thyroiditis is characterized by diffuse, painless thyroid enlargement, often with symptoms of hypothyroidism (eg, fatigue, cold intolerance). Biopsy reveals diffuse lymphocytic infiltration with formation of germinal centers.

Educational objective:
Subacute granulomatous (de Quervain) thyroiditis is characterized by painful thyroid enlargement and usually follows a viral illness. Biopsy shows a mixed inflammatory infiltrate with macrophages and multinucleated giant cells.

https://t.me/USMLEWorldStep1

CRP = C-reactive protein; **ESR** = erythrocyte sedimentation rate; **TPO** = thyroid peroxidase.

This p
called
reactir
experi
thyroic
thyroic

SGT is
progre
cells.
erythro

(Choi
(psam
and te

(Choi
surrou

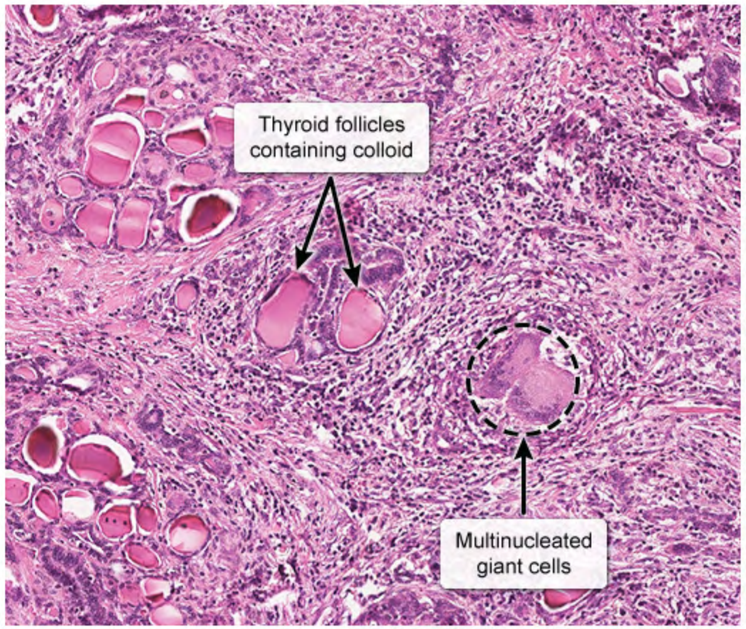
(Choi
Grave

(Choi
often v
infiltrat

Educa
Subac
follows
cells.

Exhibit Display

Granulomatous (de Quervain) thyroiditis



©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

CRP = C-reactive protein; **ESR** = erythrocyte sedimentation rate; **TPO** = thyroid peroxidase.

This p
called
reactir
experi
thyroic
thyroic

SGT is
progre
cells.
erythro

(Choi
(psam
and te

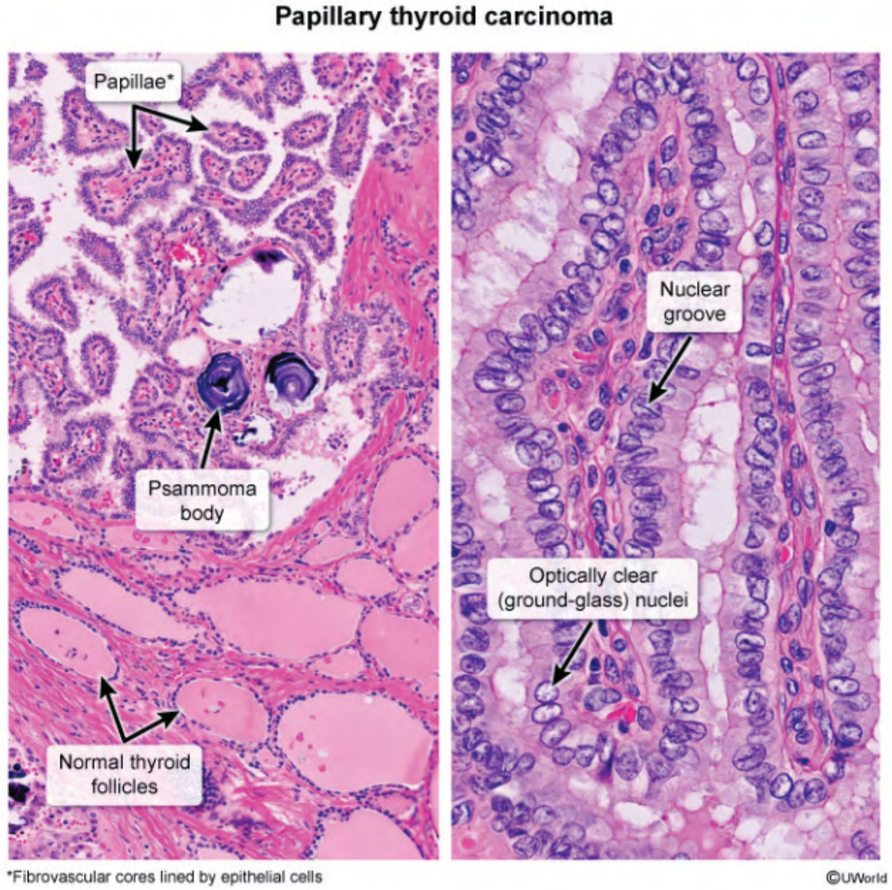
(Choi
surrou

(Choi
Grave

(Choi
often v
infiltrat

Educa
Subac
follows
cells.

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

CRP = C-reactive protein; **ESR** = erythrocyte sedimentation rate; **TPO** = thyroid peroxidase.

This p
called
reactir
experi
thyroic
thyroic

SGT is
progre
cells.
erythro

(Choi
(psam
and te

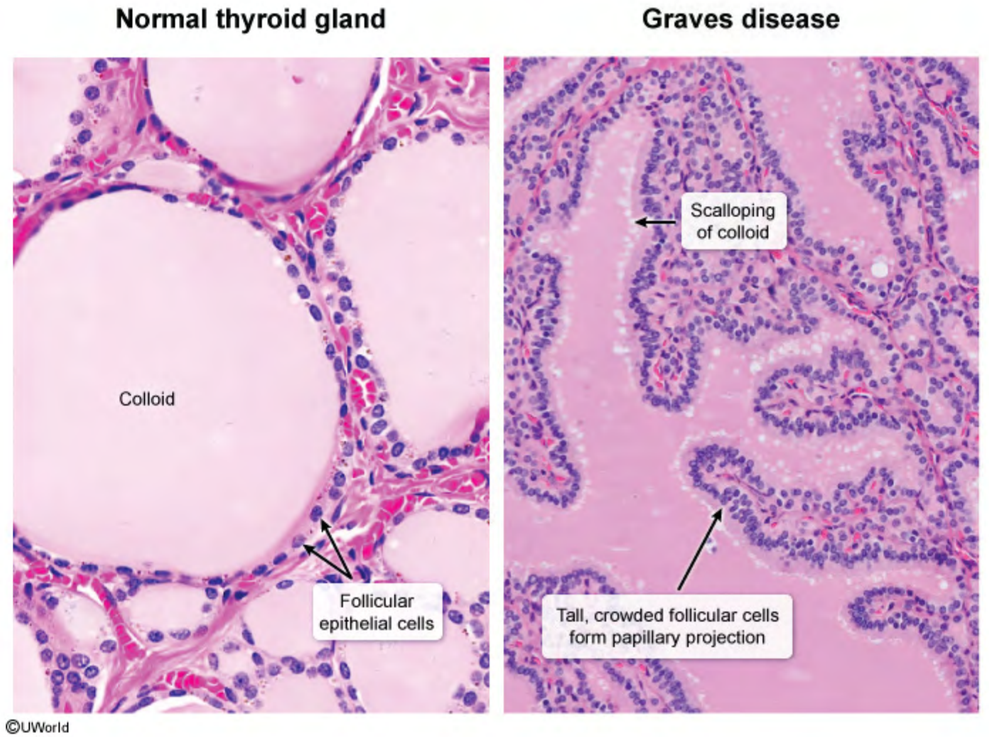
(Choi
surrou

(Choi
Grave

(Choi
often v
infiltrat

Educa
Subac
follows
cells.

Exhibit Display



Zoom In Zoom Out Reset New | Existing My Notebook

https://t.me/USMLEWorldStep1

CRP = C-reactive protein; **ESR** = erythrocyte sedimentation rate; **TPO** = thyroid peroxidase.

This p
called
reactir
experi
thyroic
thyroic

SGT is
progre
cells.
erythro

(Choi
(psam
and te

(Choi
surrou

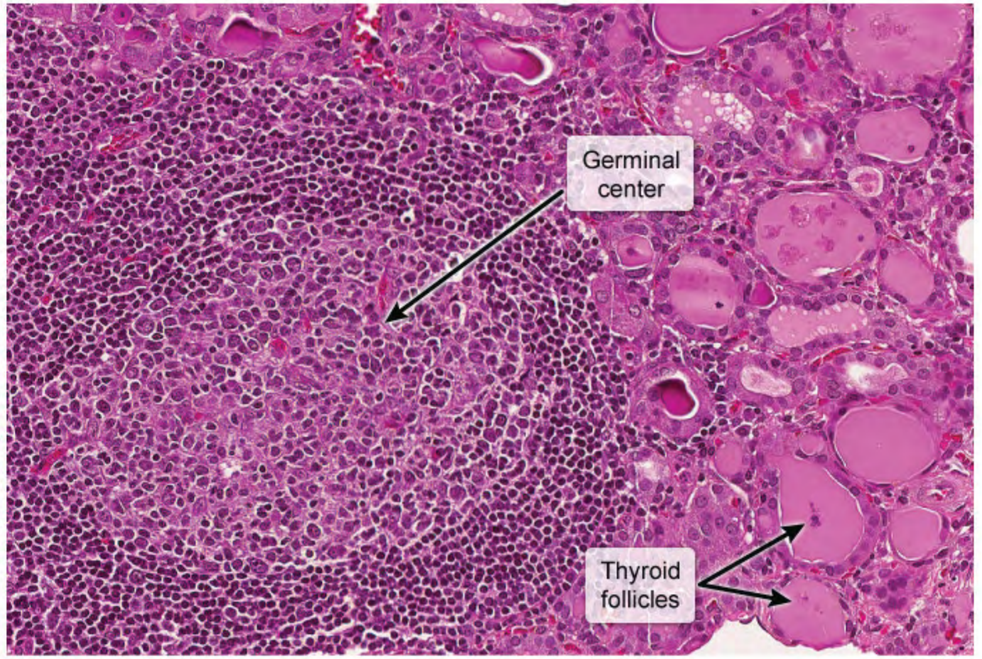
(Choi
Grave

(Choi
often v
infiltrat

Educa
Subac
follows
cells.

Exhibit Display

Hashimoto thyroiditis



©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

A 70-year-old woman comes to the office due to acute midthoracic back pain that started after a ground-level fall. The patient has also had weakness and weight loss for the past 2 months. Blood pressure is 150/70 mm Hg and pulse is 110/min. Examination shows sweaty palms and a fine hand tremor. Laboratory evaluation reveals normal hemoglobin, serum calcium, serum creatinine, and 25-hydroxyvitamin D levels. Serum thyrotropin (TSH) is undetectable. X-ray reveals a compression fracture of the T7 vertebra with diffuse demineralization of the bones. Which of the following is most likely responsible for the bone abnormalities in this patient?

- A. Decreased bone formation due to inhibition of osteoblast differentiation
- B. Decreased mineralization of bone matrix
- C. Increased bone resorption due to increased calcitonin release
- D. Increased bone resorption due to stimulation of osteoclasts
- E. Interleukin-1–induced uncoupling of bone resorption and formation

Submit

https://t.me/USMLEWorldStep1

A 70-year-old woman comes to the office due to acute midthoracic back pain that started after a ground-level fall. The patient has also had weakness and weight loss for the past 2 months. Blood pressure is 150/70 mm Hg and pulse is 110/min. Examination shows sweaty palms and a fine hand tremor. Laboratory evaluation reveals normal hemoglobin, serum calcium, serum creatinine, and 25-hydroxyvitamin D levels. Serum thyrotropin (TSH) is undetectable. X-ray reveals a compression fracture of the T7 vertebra with diffuse demineralization of the bones. Which of the following is most likely responsible for the bone abnormalities in this patient?

- A. Decreased bone formation due to inhibition of osteoblast differentiation (14%)
- ✗ B. Decreased mineralization of bone matrix (16%)
- C. Increased bone resorption due to increased calcitonin release (7%)
- ✓ D. Increased bone resorption due to stimulation of osteoclasts (54%)
- E. Interleukin-1–induced uncoupling of bone resorption and formation (7%)

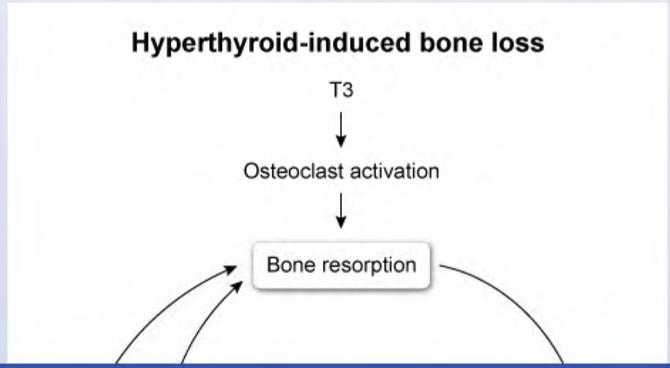
Incorrect
Correct answer
D

54%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation



https://t.me/USMLEWorldStep1

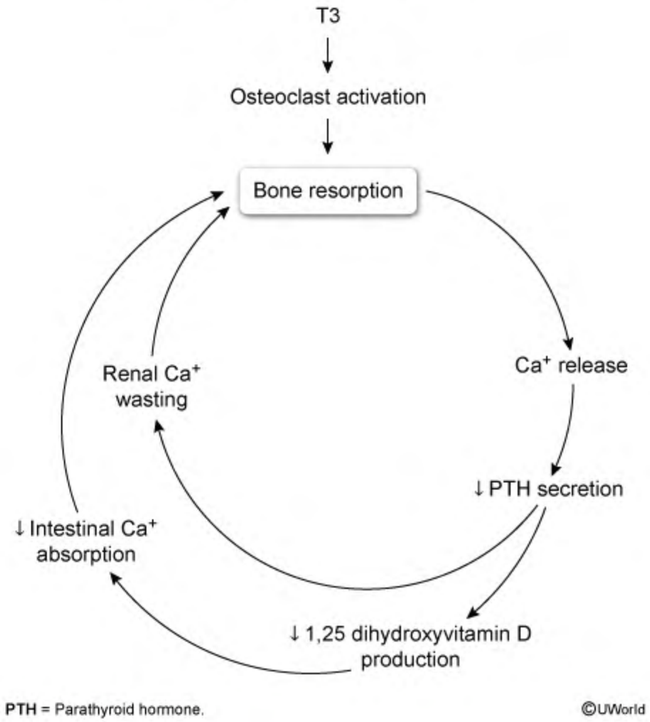
A 70-year-old woman comes to the office due to acute midthoracic back pain that started after a ground-level fall.
The pa
pulse i
hemog
undete
Which

Inco
Corre
D

Expl

Exhibit Display

Hyperthyroid-induced bone loss



PTH = Parathyroid hormone.

©UWorld

Zoom In Zoom Out Reset New | Existing My Notebook

https://t.me/USMLEWorldStep1

This patient has **hyperthyroidism**, presenting with weight loss, tremor, tachycardia, and a suppressed TSH level. In addition, she has an acute vertebral compression fracture and diffuse bone mineral loss consistent with **osteoporosis**.

Hyperthyroidism causes increased bone turnover with **net bone loss**. The bone loss in hyperthyroidism is driven by **triiodothyronine (T3)**, the more active form of thyroid hormone that is generated primarily by deiodination of thyroxine (T4) in peripheral tissues. T3 stimulates osteoclast differentiation, **increased bone resorption**, and release of calcium.

As calcium is released from the bones into the circulation, it suppresses parathyroid hormone (PTH) secretion, which leads to decreased reabsorption of calcium in the renal tubules and gut. This maintains **normal blood calcium levels** as bone mineralization is progressively depleted.

(Choice A) Thyroid hormone stimulates (not inhibits) osteoblast differentiation and activity, leading to increased formation of new bone. However, in the hyperthyroid state, this effect is outweighed by a greater increase in bone loss.

(Choice B) Mineralization of bone matrix is regulated directly by local concentrations of calcium and inorganic phosphate and indirectly by multiple endocrine and paracrine factors (eg, PTH, vitamin D). Although vitamin D deficiency can cause osteomalacia due to impaired mineralization, thyroid hormone has only a minor effect on this process.

(Choice C) Calcitonin is released by the parafollicular cells of the thyroid. It inhibits osteoclast activity, leading to decreased (not increased) bone resorption. Calcitonin is regulated primarily by circulating calcium levels, not thyroid hormone.

(Choice E) In addition to causing lytic bone lesions, multiple myeloma causes diffuse bone loss due to interleukin-1–induced uncoupling of bone resorption and formation (ie, increased osteoclast activity without a restorative osteoblast action).

Educational objective:
Hyperthyroidism causes increased bone turnover with net bone loss, potentially leading to osteoporosis. The bone loss is driven by triiodothyronine, which stimulates osteoclast differentiation, increased bone resorption, and

https://t.me/USMLEWorldStep1

Hyperthyroidism causes increased bone turnover with **net bone loss**. The bone loss in hyperthyroidism is driven by **triiodothyronine (T3)**, the more active form of thyroid hormone that is generated primarily by deiodination of thyroxine (T4) in peripheral tissues. T3 stimulates osteoclast differentiation, **increased bone resorption**, and release of calcium.

As calcium is released from the bones into the circulation, it suppresses parathyroid hormone (PTH) secretion, which leads to decreased reabsorption of calcium in the renal tubules and gut. This maintains **normal blood calcium levels** as bone mineralization is progressively depleted.

(Choice A) Thyroid hormone stimulates (not inhibits) osteoblast differentiation and activity, leading to increased formation of new bone. However, in the hyperthyroid state, this effect is outweighed by a greater increase in bone loss.

(Choice B) Mineralization of bone matrix is regulated directly by local concentrations of calcium and inorganic phosphate and indirectly by multiple endocrine and paracrine factors (eg, PTH, vitamin D). Although vitamin D deficiency can cause osteomalacia due to impaired mineralization, thyroid hormone has only a minor effect on this process.

(Choice C) Calcitonin is released by the parafollicular cells of the thyroid. It inhibits osteoclast activity, leading to decreased (not increased) bone resorption. Calcitonin is regulated primarily by circulating calcium levels, not thyroid hormone.

(Choice E) In addition to causing lytic bone lesions, multiple myeloma causes diffuse bone loss due to interleukin-1–induced uncoupling of bone resorption and formation (ie, increased osteoclast activity without a restorative osteoblast action).

Educational objective:
Hyperthyroidism causes increased bone turnover with net bone loss, potentially leading to osteoporosis. The bone loss is driven by triiodothyronine, which stimulates osteoclast differentiation, increased bone resorption, and release of calcium.

Physiology	Endocrine, Diabetes & Metabolism	Hyperthyroidism
Subject	System	Topic

https://t.me/USMLEWorldStep1

This patient has **hyperthyroidism**, presenting with weight loss, tremor, tachycardia, and a suppressed TSH level.

In add
osteo

Hyper
by **trii**
thyrox
releas

As cal
which
calciu

(Choi
format
loss.

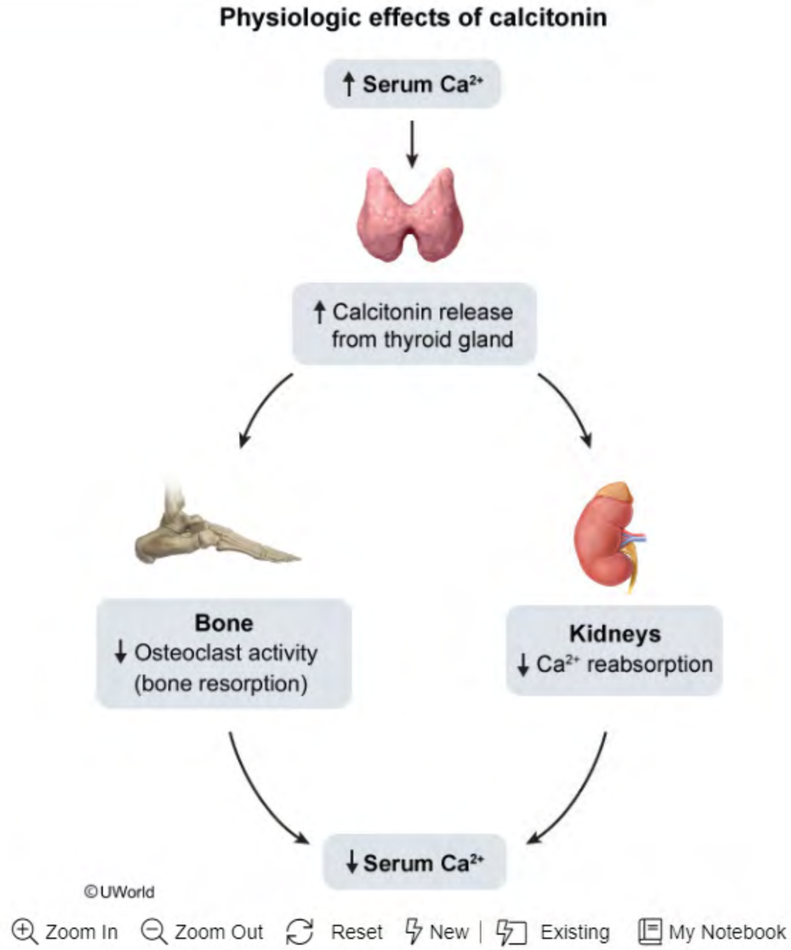
(Choi
phosp
deficie
proces

(Choi
decrea
thyroid

(Choi
1–indu
osteob

Educa
Hyper
loss is driven by triiodothyronine, which stimulates osteoclast differentiation, increased bone resorption, and

Exhibit Display



Zoom In Zoom Out Reset New | Existing My Notebook

https://t.me/USMLEWorldStep1

This patient has **hyperthyroidism**, presenting with weight loss, tremor, tachycardia, and a suppressed TSH level.

In add
osteo

Hyper
by **trii**
thyrox
releas

As cal
which
calciu

(Choi
format
loss.

(Choi
phosp
deficie
proces

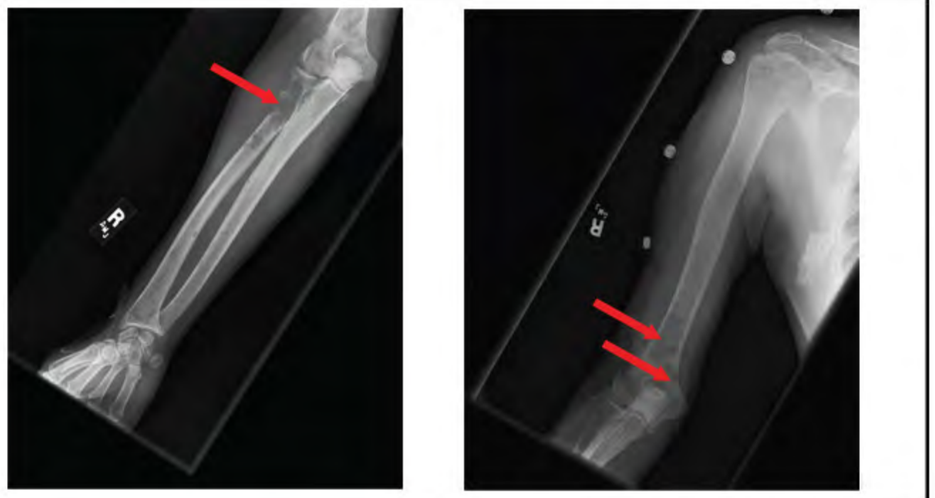
(Choi
decrea
thyroic

(Choi
1–indu
osteob

Educa
Hyper
loss is driven by triiodothyronine, which stimulates osteoclast differentiation, increased bone resorption, and

Exhibit Display

Osteolytic bony metastases in multiple myeloma



©UWorld

Zoom In
Zoom Out
Reset
New | Existing
My Notebook

https://t.me/USMLEWorldStep1

A 27-year-old man comes to the office due to recurrent episodes of muscle weakness. He has no other significant medical history. The patient's weight has been stable for the past few years with a BMI of 23 kg/m^2. Blood pressure is 190/110 mm Hg supine and 195/110 mm Hg standing. Pulse is 70/min supine and 72/min standing. The rest of the physical examination is unremarkable. Laboratory evaluation shows very low plasma renin levels. Overactivity of which of the following is most likely responsible for this patient's symptoms?

- A. Chromaffin cells of the adrenals
- B. Extraadrenal paraganglion cells
- C. Juxtaglomerular cells of the kidney
- D. Zona fasciculata of the adrenals
- E. Zona glomerulosa of the adrenals
- F. Zona reticularis of the adrenals

Submit

https://t.me/USMLEWorldStep1

A 27-year-old man comes to the office due to recurrent episodes of muscle weakness. He has no other significant medical history. The patient's weight has been stable for the past few years with a BMI of 23 kg/m^2. Blood pressure is 190/110 mm Hg supine and 195/110 mm Hg standing. Pulse is 70/min supine and 72/min standing. The rest of the physical examination is unremarkable. Laboratory evaluation shows very low plasma renin levels. Overactivity of which of the following is most likely responsible for this patient's symptoms?

- ✗ A. Chromaffin cells of the adrenals (9%)
- B. Extraadrenal paraganglion cells (0%)
- C. Juxtaglomerular cells of the kidney (7%)
- D. Zona fasciculata of the adrenals (9%)
- ✓ E. Zona glomerulosa of the adrenals (70%)
- F. Zona reticularis of the adrenals (2%)

Incorrect
Correct answer
E

70%
Answered correctly

12 secs
Time Spent

2023
Version

Explanation

Adrenal cortical structure & function

Principal stimulatory hormone	Adrenal layer	Principal secreted hormone	Physiologic effect
Angiotensin II	Zona glomerulosa	Aldosterone	↑ Blood volume

https://t.me/USMLEWorldStep1

A 27-year-old man comes to the office due to recurrent episodes of muscle weakness. He has no other significant
medic
pressu
The re
Overa

Exhibit Display

Adrenal cortical structure & function

Principal stimulatory hormone	Adrenal layer	Principal secreted hormone	Physiologic effect
Angiotensin II	Zona glomerulosa	Aldosterone	↑ Blood volume
ACTH	Zona fasciculata	Cortisol	↑ Vascular tone ↑ Blood glucose
ACTH	Zona reticularis	Androgens	Libido & pubic hair in women
	Medulla		

©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

©UWorld

This patient's onset of **hypertension** at a young age is suggestive of a secondary underlying cause; his low plasma renin levels most likely indicate primary hyperaldosteronism (Conn syndrome), which is characterized by autonomous aldosterone secretion from the **zona glomerulosa** of the adrenal cortex. Bilateral adrenal hyperplasia is the most common cause, followed by a unilateral adrenal adenoma.

Aldosterone, which is normally regulated by angiotensin II and K^+ levels, stimulates reabsorption of sodium (Na^+) and secretion of potassium (K^+) and hydrogen (H^+) in the renal collecting ducts. Excess aldosterone causes Na^+ retention, hypertension, and feedback suppression of the renin-angiotensin system (ie, **low renin activity**). Some patients also develop metabolic alkalosis and **hypokalemia**. Symptomatic hypokalemia may cause **muscle weakness**, cramps, and, occasionally, rhabdomyolysis and cardiac arrhythmias.

Despite increased Na^+ reabsorption, extravascular volume overload (eg, peripheral edema) is rarely seen due to a phenomenon known as aldosterone escape. With aldosterone escape, increased intravascular volume increases pressure natriuresis and augments atrial natriuretic peptide release, thereby limiting net Na^+ retention and extravascular volume overload. Hypernatremia is also not typically seen because the temporary increase in serum osmolality triggers a compensatory rise in antidiuretic hormone release.

(Choices A and B) Pheochromocytomas are catecholamine-secreting tumors arising from the chromaffin cells of the adrenal medulla or extraadrenal sympathetic chain that typically present with severe hypertension. Pheochromocytomas stimulate the renin-angiotensin system due to high circulating catecholamine levels and are associated with tachycardia and symptoms of catecholamine excess (eg, sweating, palpitations, headache).

(Choice C) Increased renin production by the juxtaglomerular apparatus leads to hypertension with elevated aldosterone levels. This typically occurs in the setting of renal artery stenosis due to decreased renal blood flow. However, this patient's renin activity is suppressed.

(Choices D and F) Hypersecretion from cells of the zona fasciculata or zona reticularis would lead to Cushing syndrome or hyperandrogenism, respectively. Cushing syndrome can cause hypertension and hypokalemia but is usually associated with weight gain and a cushingoid body habitus (eg, central obesity, moon facies). Clinical manifestations of adrenal hyperandrogenism are typically minimal in men because androgen levels are already high due to testicular testosterone production.

https://t.me/USMLEWorldStep1

and secretion of potassium (K^+) and hydrogen (H^+) in the renal collecting ducts. Excess aldosterone causes Na^+ retention, hypertension, and feedback suppression of the renin-angiotensin system (ie, **low renin activity**). Some patients also develop metabolic alkalosis and **hypokalemia**. Symptomatic hypokalemia may cause **muscle weakness**, cramps, and, occasionally, rhabdomyolysis and cardiac arrhythmias.

Despite increased Na^+ reabsorption, extravascular volume overload (eg, peripheral edema) is rarely seen due to a phenomenon known as aldosterone escape. With aldosterone escape, increased intravascular volume increases pressure natriuresis and augments atrial natriuretic peptide release, thereby limiting net Na^+ retention and extravascular volume overload. Hypernatremia is also not typically seen because the temporary increase in serum osmolality triggers a compensatory rise in antidiuretic hormone release.

(Choices A and B) Pheochromocytomas are catecholamine-secreting tumors arising from the chromaffin cells of the adrenal medulla or extraadrenal sympathetic chain that typically present with severe hypertension. Pheochromocytomas stimulate the renin-angiotensin system due to high circulating catecholamine levels and are associated with tachycardia and symptoms of catecholamine excess (eg, sweating, palpitations, headache).

(Choice C) Increased renin production by the juxtaglomerular apparatus leads to hypertension with elevated aldosterone levels. This typically occurs in the setting of renal artery stenosis due to decreased renal blood flow. However, this patient's renin activity is suppressed.

(Choices D and F) Hypersecretion from cells of the zona fasciculata or zona reticularis would lead to Cushing syndrome or hyperandrogenism, respectively. Cushing syndrome can cause hypertension and hypokalemia but is usually associated with weight gain and a cushingoid body habitus (eg, central obesity, moon facies). Clinical manifestations of adrenal hyperandrogenism are typically minimal in men because androgen levels are already high due to testicular testosterone production.

Educational objective:
Primary hyperaldosteronism is caused by excessive aldosterone secretion, typically due to an aldosterone-producing adrenal adenoma or bilateral nodular hyperplasia of the zona glomerulosa. Clinical findings include hypertension, low plasma renin, hypokalemia, and metabolic alkalosis.

Pathophysiology	Endocrine, Diabetes & Metabolism	Hyperaldosteronism
Subject	System	Topic

https://t.me/USMLEWorldStep1

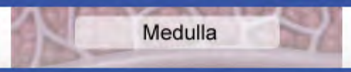


Exhibit Display

Primary hyperaldosteronism (Conn syndrome)	
Clinical features	• Bilateral adrenal hyperplasia (~60%) or unilateral adenoma • Difficult-to-control hypertension • Hypokalemia & metabolic alkalosis* • No extravascular volume overload (aldosterone escape)
Diagnosis	• Elevated plasma aldosterone & low plasma renin (ratio >20) • Absence of aldosterone suppression with oral saline load • CT scan of adrenal glands to determine bilateral hyperplasia vs adenoma
Treatment	• Bilateral adrenal hyperplasia: MRA (eg, spironolactone) • Unilateral adenoma: surgical resection preferred
*In some patients, the characteristic electrolyte abnormalities are apparent only after a thiazide is initiated for blood pressure management. **MRA** = mineralocorticoid receptor antagonist.	

New | Existing | My Notebook

This p
plasm
autono
hyperp

Aldos
and se
retenti
patien
weakr

Despit
pheno
pressu
extrav
osmol

(Choi
the ad
Pheoc
associ

(Choi
aldost
Howev

(Choices D and F) Hypersecretion from cells of the zona fasciculata or zona reticularis would lead to Cushing

https://t.me/USMLEWorldStep1

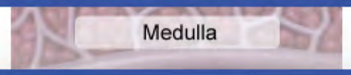
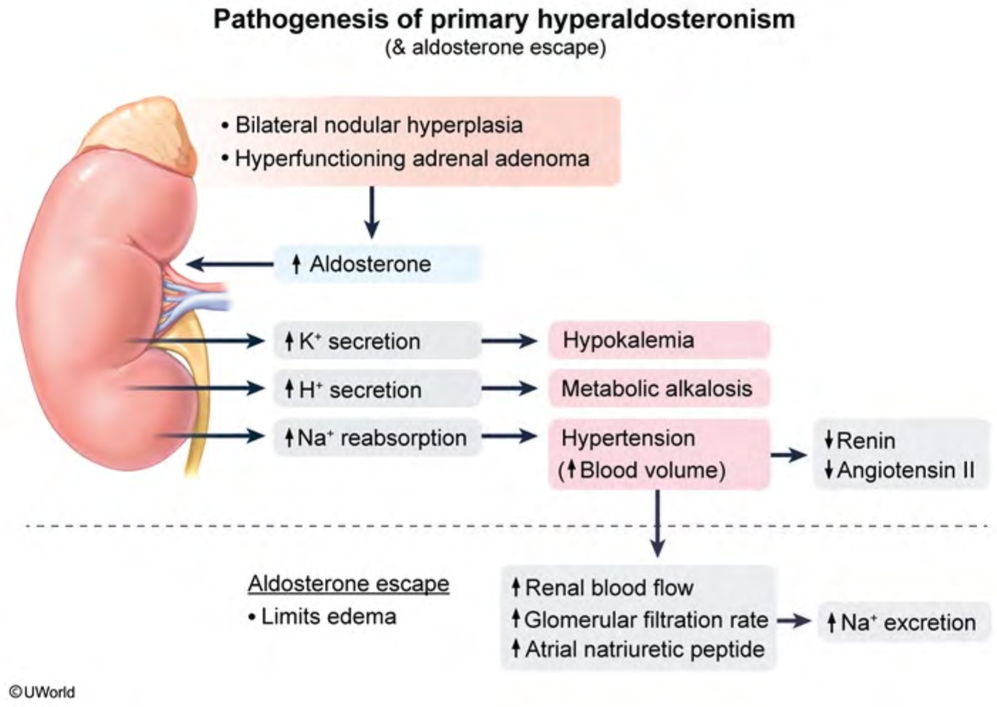


Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

This p
plasm
autonc
hyperp

Aldos
and se
retenti
patien
weakr

Despit
pheno
pressu
extrav
osmol

(Choi
the ad
Pheoc
associ

(Choi
aldost
Howev

(Choices D and F) Hypersecretion from cells of the zona fasciculata or zona reticularis would lead to Cushing

https://t.me/USMLEWorldStep1

A 50-year-old female presents with abdominal pain, diarrhea, and weight loss. She was diagnosed with diabetes mellitus two months ago. Her serum somatostatin level is highly elevated. Further evaluation reveals biliary stones. Suppression of which of the following hormones is most likely responsible for biliary stones?

- A. Secretin
- B. Cholecystokinin
- C. Glucagon
- D. Insulin
- E. Gastrin
- F. Growth hormone

Submit

https://t.me/USMLEWorldStep1

A 50-year-old female presents with abdominal pain, diarrhea, and weight loss. She was diagnosed with diabetes mellitus two months ago. Her serum somatostatin level is highly elevated. Further evaluation reveals biliary stones. Suppression of which of the following hormones is most likely responsible for biliary stones?

- A. Secretin (4%)
- ✓ B. Cholecystokinin (87%)
- C. Glucagon (2%)
- D. Insulin (2%)
- E. Gastrin (2%)
- F. Growth hormone (2%)

Correct | 87% Answered correctly | 03 secs Time Spent | 2023 Version

Explanation

The term somatostatin was originally applied to the 14-aminoacid cyclic peptide that is secreted by the hypothalamus and that inhibits the production of growth hormone from the anterior pituitary gland. Somatostatin is now known to be secreted from other parts of the central nervous system and from pancreatic delta cells. Somatostatin secreted from pancreatic "delta cells" decreases the secretion of secretin, cholecystokinin, glucagon, insulin, and gastrin. Somatostatinomas are rare pancreatic islet cell tumors that arise from delta cells. Patients with somatostatinomas present with hyperglycemia or hypoglycemia, steatorrhea (excessive fat in the feces), and gallbladder stones. Gallbladder stones form because of poor gallbladder contractility, which is secondary to inhibition of cholecystokinin release.

(Choices C and D) Somatostatin decreases the release of glucagon as well as insulin. However, the secretion of insulin is more profoundly inhibited than is glucagon; therefore, the net result is hyperglycemia.

https://t.me/USMLEWorldStep1

Explanation

The term somatostatin was originally applied to the 14-aminoacid cyclic peptide that is secreted by the hypothalamus and that inhibits the production of growth hormone from the anterior pituitary gland. Somatostatin is now known to be secreted from other parts of the central nervous system and from pancreatic delta cells. Somatostatin secreted from pancreatic "delta cells" decreases the secretion of secretin, cholecystokinin, glucagon, insulin, and gastrin. Somatostatinomas are rare pancreatic islet cell tumors that arise from delta cells. Patients with somatostatinomas present with hyperglycemia or hypoglycemia, steatorrhea (excessive fat in the feces), and gallbladder stones. Gallbladder stones form because of poor gallbladder contractility, which is secondary to inhibition of cholecystokinin release.

(Choices C and D) Somatostatin decreases the release of glucagon as well as insulin. However, the secretion of insulin is more profoundly inhibited than is glucagon; therefore, the net result is hyperglycemia.

(Choice A) Steatorrhea results from the decreased secretion of secretin as well as a decrease in gastrointestinal motility.

(Choice E) A decrease in gastrin release causes hypochlorhydria.

(Choice F) As indicated above, somatostatin does decrease growth hormone secretion from the normal pituitary gland, and it does so in growth-hormone-secreting pituitary adenomas. However, somatostatin cannot be used in clinical practice because of its extremely short half-life. Somatostatin analogs (octreotide and lanreotide) have a longer plasma half-life and are available for clinical use.

Educational Objective:
Reduced gallbladder contractility, due to decreased cholecystokinin secretion, is responsible for biliary stones in patients with somatostatinoma.

Pathophysiology	Endocrine, Diabetes & Metabolism	Gastrointestinal hormones
Subject	System	Topic

Copyright © UWorld. All rights reserved.

https://t.me/USMLEWorldStep1

A nuclear waste disposal plant suffers a containment failure and several grams of iodine-131 are released into the local environment. A number of workers are believed to have been exposed to dangerous levels of the radioactive material. Which of the following should be immediately administered to help prevent tissue damage in these individuals?

- A. Levothyroxine
- B. Potassium iodide
- C. Prednisone
- D. Propranolol
- E. Propylthiouracil

Submit

https://t.me/USMLEWorldStep1

A nuclear waste disposal plant suffers a containment failure and several grams of iodine-131 are released into the local environment. A number of workers are believed to have been exposed to dangerous levels of the radioactive material. Which of the following should be immediately administered to help prevent tissue damage in these individuals?

- ✗ A. Levothyroxine (6%)
- ✓ B. Potassium iodide (67%)
- C. Prednisone (1%)
- D. Propranolol (1%)
- E. Propylthiouracil (23%)

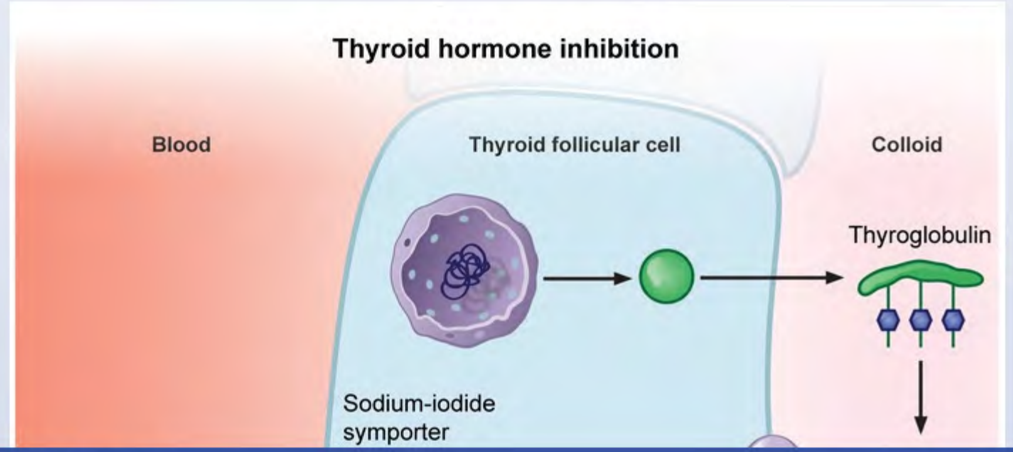
Incorrect
Correct answer
B

67%
Answered correctly

03 secs
Time Spent

2023
Version

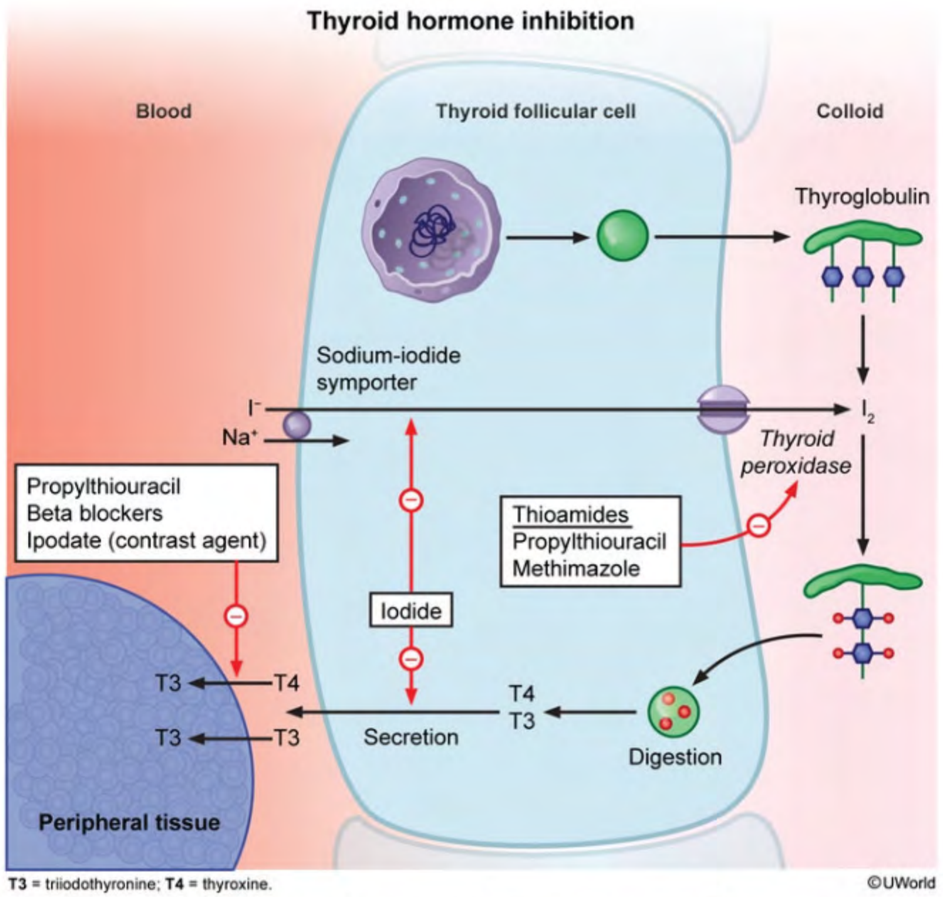
Explanation



https://t.me/USMLEWorldStep1

A nuclear waste disposal plant suffers a containment failure and several grams of iodine-131 are released into the local e
materi
individ

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Sodium-iodide symporter

https://t.me/USMLEWorldStep1

T3 = triiodothyronine; **T4** = thyroxine.

©UWorld

Radioactive material such as **iodine-131 (^{131}I)** can be released into the environment following nuclear reactor accidents, breach-of-containment at waste disposal sites, or atomic bomb blasts. Like non-radioactive iodine, ^{131}I is preferentially taken up and concentrated within the **thyroid gland**. There it can cause significant tissue damage that may result in radiation-induced hypothyroidism and **thyroid carcinoma** (particularly in younger patients). In the event of a nuclear accident, **potassium iodide** is given prophylactically to protect the thyroid from excessive accumulation of radioactive ^{131}I.

Energy-dependent transport of inorganic iodide into the thyroid follicular cell (iodide trapping) is accomplished by the sodium-iodide symporter located on the basolateral membrane. Because this transporter takes up all isotopes of iodide (as well as other ions such as perchlorate and pertechnetate), high serum levels of nonradioactive iodide can **competitively inhibit** radioactive I^{131} from entering thyroid follicular cells. Large increases in serum iodide levels also inhibit iodine organification (Wolff-Chaikoff effect) and reduce thyroid hormone release.

(Choice A) Levothyroxine is a synthetic form of T4 used to treat hypothyroidism. High doses of levothyroxine suppress TSH, just as high amounts of natural T4 would. Because TSH stimulates iodine trapping, high doses of levothyroxine would ultimately reduce iodine uptake in the thyroid follicular cells. However, this regulatory process requires several days to weeks to take effect.

(Choices C and D) Propranolol is used to reduce the adrenergic effects of thyrotoxicosis (eg, tachycardia, tremor). Prednisone is used to reduce lymphocyte-mediated inflammatory effects in Graves ophthalmopathy. However, neither propranolol nor prednisone affects the uptake of iodine in thyroid follicular cells.

(Choice E) Propylthiouracil is used in the treatment of hyperthyroidism and decreases formation of thyroid hormone by inhibiting the enzyme thyroid peroxidase. Although inhibition of iodine organification will cause decreased iodide uptake by the thyroid, potassium iodide promotes this effect more rapidly and efficiently by also acting as a competitive inhibitor for iodide entry into the cell.

Educational objective:
Potassium iodide competitively inhibits thyroid uptake of radioactive iodine isotopes and is often administered following nuclear accidents to protect the thyroid and prevent development of radiation-induced thyroid carcinoma.

https://t.me/USMLEWorldStep1

A 38-year-old man comes to the office with headaches, loss of libido, and erectile dysfunction for the last 3 months. The patient has no chronic medical conditions and takes no prescription or over-the-counter medications. He does not use tobacco, alcohol, or illicit drugs. Vital signs are normal. The examination is notable for peripheral vision loss, bilateral gynecomastia, and soft testes without masses. Laboratory evaluation shows normal serum prolactin, normal β-hCG, low serum LH, and low serum testosterone. Which of the following is the most likely mechanism for this patient's gynecomastia?

- A. Decreased systemic clearance of estrogen
- B. Defective androgen receptor function
- C. Enzymatic defect in the testosterone biosynthetic pathway
- D. Excessive estrogen production in the testes
- E. Persistent aromatization of adrenal estrogen precursors

Submit

https://t.me/USMLEWorldStep1

A 38-year-old man comes to the office with headaches, loss of libido, and erectile dysfunction for the last 3 months. The patient has no chronic medical conditions and takes no prescription or over-the-counter medications. He does not use tobacco, alcohol, or illicit drugs. Vital signs are normal. The examination is notable for peripheral vision loss, bilateral gynecomastia, and soft testes without masses. Laboratory evaluation shows normal serum prolactin, normal β-hCG, low serum LH, and low serum testosterone. Which of the following is the most likely mechanism for this patient's gynecomastia?

- A. Decreased systemic clearance of estrogen (7%)
- ✗ B. Defective androgen receptor function (10%)
- C. Enzymatic defect in the testosterone biosynthetic pathway (16%)
- D. Excessive estrogen production in the testes (13%)
- ✓ E. Persistent aromatization of adrenal estrogen precursors (51%)

Incorrect
Correct answer
E

51%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

This patient's headaches and peripheral vision loss (ie, bitemporal hemianopsia) suggest a **pituitary mass** with compression of the optic chiasm. In addition, he has features of hypogonadism, including decreased libido, erectile dysfunction, testicular atrophy, and a low circulating testosterone level; his low LH level confirms secondary (central) hypogonadism.

Secondary hypogonadism is common in patients with pituitary masses. Potential etiologies include the following:

- High prolactin levels from a prolactin-secreting adenoma (prolactinoma) can suppress secretion of GnRH, leading to decreased LH secretion and lower testosterone production
- Non-prolactin-secreting tumors can disrupt the inhibitory dopaminergic regulation of prolactin secretion

https://t.me/USMLEWorldStep1

Explanation

This patient's headaches and peripheral vision loss (ie, bitemporal hemianopsia) suggest a **pituitary mass** with compression of the optic chiasm. In addition, he has features of hypogonadism, including decreased libido, erectile dysfunction, testicular atrophy, and a low circulating testosterone level; his low LH level confirms secondary (central) hypogonadism.

Secondary hypogonadism is common in patients with pituitary masses. Potential etiologies include the following:

- High prolactin levels from a prolactin-secreting adenoma (prolactinoma) can suppress secretion of GnRH, leading to decreased LH secretion and lower testosterone production
- Non–prolactin-secreting tumors can disrupt the inhibitory dopaminergic regulation of prolactin secretion, leading to hyperprolactinemia and (usually mild) hypogonadism
- Direct **compression of gonadotrope cells** with loss of LH secretion (independent of prolactin effect), which is likely in this patient with a normal prolactin level

Gynecomastia is the abnormal growth of male breast tissue, typically due to an **increased estrogen/testosterone ratio**. This patient has low testosterone, but production of estrogen precursors (eg, androstenedione, dehydroepiandrosterone [DHEA], DHEA sulfate) continues uninterrupted in the zona reticularis of the adrenal cortex. These steroid hormones are subsequently **aromatized to estrogens** in peripheral tissues. When testosterone levels are normal, the inhibitory effect of testosterone prevents breast growth, but when testosterone is low, the adrenal-derived estrogens can produce significant gynecomastia.

(Choice A) Estrogen is cleared primarily in the liver. Patients with cirrhosis commonly develop gynecomastia due to decreased clearance of estrogen along with increased production and aromatization of estrogen precursors. However, this patient has no risk factors for cirrhosis (eg, alcohol use), and his bitemporal hemianopsia suggests a pituitary etiology.

(Choice B) Androgen receptor defects typically present at birth with a female phenotype or ambiguous genitalia (with 46,XY karyotype), although some variants (partial androgen insensitivity syndrome) may present in adulthood

https://t.me/USMLEWorldStep1

- Direct **compression of gonadotrope cells** with loss of LH secretion (independent of prolactin effect), which is likely in this patient with a normal prolactin level

Gynecomastia is the abnormal growth of male breast tissue, typically due to an **increased estrogen/testosterone ratio**. This patient has low testosterone, but production of estrogen precursors (eg, androstenedione, dehydroepiandrosterone [DHEA], DHEA sulfate) continues uninterrupted in the zona reticularis of the adrenal cortex. These steroid hormones are subsequently **aromatized to estrogens** in peripheral tissues. When testosterone levels are normal, the inhibitory effect of testosterone prevents breast growth, but when testosterone is low, the adrenal-derived estrogens can produce significant gynecomastia.

(Choice A) Estrogen is cleared primarily in the liver. Patients with cirrhosis commonly develop gynecomastia due to decreased clearance of estrogen along with increased production and aromatization of estrogen precursors. However, this patient has no risk factors for cirrhosis (eg, alcohol use), and his bitemporal hemianopsia suggests a pituitary etiology.

(Choice B) Androgen receptor defects typically present at birth with a female phenotype or ambiguous genitalia (with 46,XY karyotype), although some variants (partial androgen insensitivity syndrome) may present in adulthood with gynecomastia and undervirilization (eg, decreased facial and pubic hair). However, androgen production is unaffected, and testosterone levels would be normal to high.

(Choice C) Testosterone biosynthetic defects generally present at birth or during development with abnormal genitalia and/or undervirilization in males. Biochemical testing shows primary hypogonadism (ie, low testosterone, high LH).

(Choice D) Estrogen is synthesized in the testes by the aromatization of androgens, producing high local concentrations. However, this patient has decreased testicular testosterone production, so subsequent estrogen synthesis would also be low.

Educational objective:
The adrenal cortex produces estrogen precursors (eg, androstenedione, dehydroepiandrosterone [DHEA], DHEA sulfate), which are subsequently aromatized to estrogens in peripheral tissues. In men with hypogonadism (low testosterone), the resulting elevation in the estrogen/testosterone ratio can produce gynecomastia.

https://t.me/USMLEWorldStep1

Expl

This p
compr
erectil
(centra

Secon

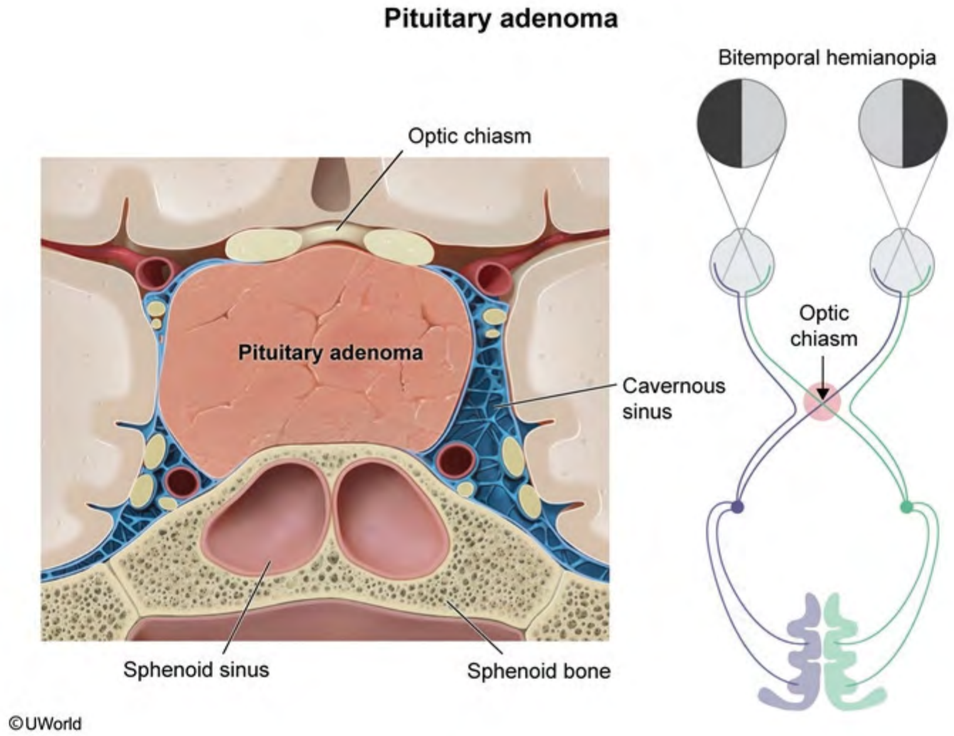
- H
  le
- N
  le
- D
  is

Gynec
estrog
andros
the ad
When
testost

(Choi
to dec
Howev
pituitar

(Choice B) Androgen receptor defects typically present at birth with a female phenotype or ambiguous genitalia (with 46,XY karyotype), although some variants (partial androgen insensitivity syndrome) may present in adulthood

Exhibit Display

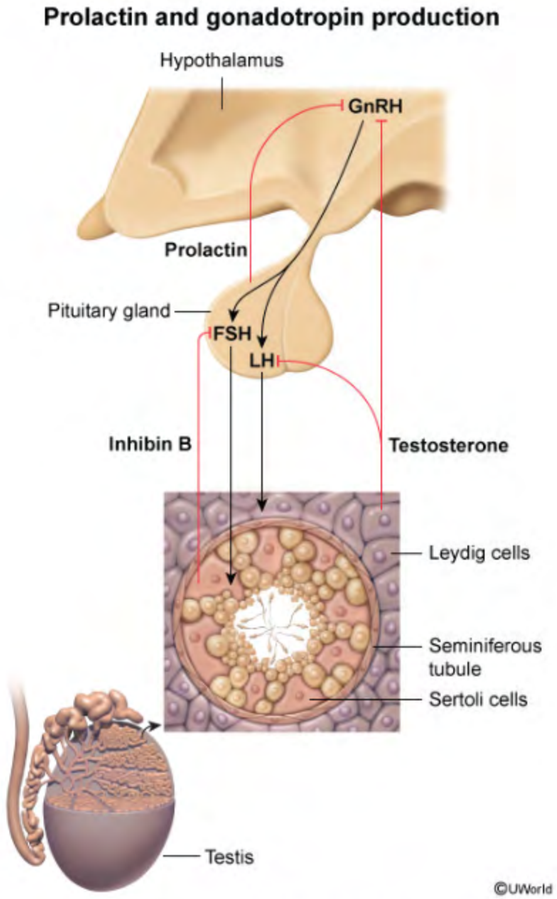


Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

Expl

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

This p
compr
erectil
(centra

Secon

- H
  le
- N
  le
- D
  is

Gynec
estrog
andros
the ad
When
testost

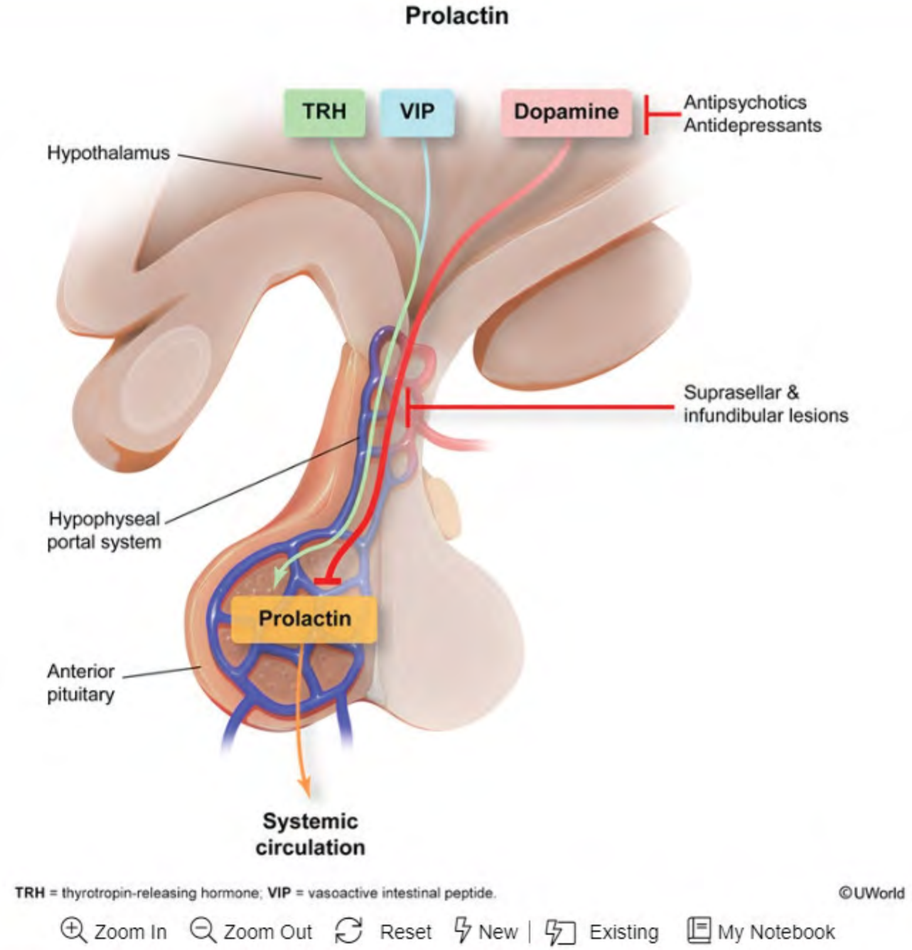
(Choi
to dec
Howev
pituitar

(Choice B) Androgen receptor defects typically present at birth with a female phenotype or ambiguous genitalia (with 46,XY karyotype), although some variants (partial androgen insensitivity syndrome) may present in adulthood

https://t.me/USMLEWorldStep1

Expl

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

This p
compr
erectil
(centra

Secon

- H
  le
- N
  le
- D
  is

Gynec
estrog
andros
the ad
When
testost

(Choi
to dec
Howev
pituitar

(Choice B) Androgen receptor defects typically present at birth with a female phenotype or ambiguous genitalia (with 46,XY karyotype), although some variants (partial androgen insensitivity syndrome) may present in adulthood

https://t.me/USMLEWorldStep1

Expl

This p
compr
erectil
(centra

Secon

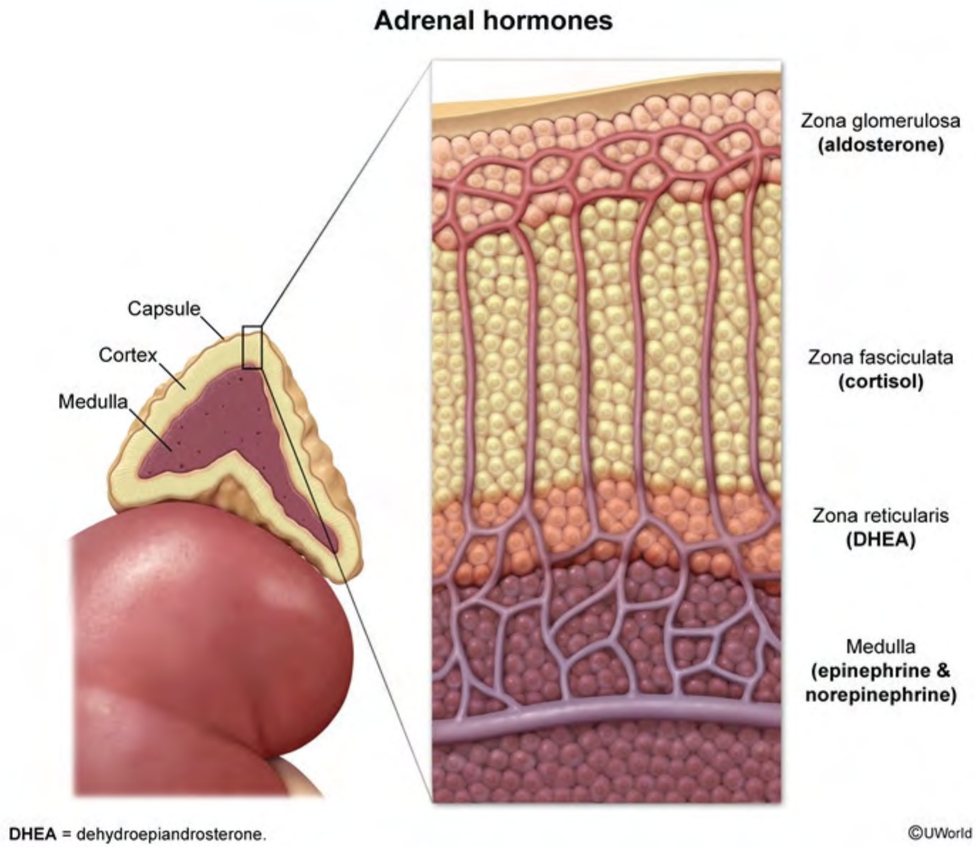
- H
  le
- N
  le
- D
  is

Gynec
estrog
andros
the ad
When
testost

(Choi
to dec
Howev
pituitar

(Choice B) Androgen receptor defects typically present at birth with a female phenotype or ambiguous genitalia (with 46,XY karyotype), although some variants (partial androgen insensitivity syndrome) may present in adulthood

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

A 56-year-old woman comes to the office due to progressive weight gain and fatigue over the last 4 months. She also has had increasing difficulty in lifting heavy objects and climbing stairs. The patient has moderate, persistent bronchial asthma for which she uses inhaled corticosteroids and beta-2 agonists. Family history is significant for colon cancer in her father. Blood pressure is 160/90 mm Hg and pulse is 80/min. On physical examination, there is symmetric proximal muscle weakness of the upper and lower extremities. Fasting plasma glucose level is 135 mg/dL and 24-hour urinary cortisol is increased. Further evaluation reveals that high-dose, but not low-dose, dexamethasone suppresses serum cortisol levels. Serum ACTH levels are high-normal. Which of the following is the most likely cause of this patient's symptoms?

- A. Adrenal adenoma
- B. Adrenal carcinoma
- C. Exogenous glucocorticoids
- D. Pituitary adenoma
- E. Small cell lung cancer

Submit

https://t.me/USMLEWorldStep1

A 56-year-old woman comes to the office due to progressive weight gain and fatigue over the last 4 months. She also has had increasing difficulty in lifting heavy objects and climbing stairs. The patient has moderate, persistent bronchial asthma for which she uses inhaled corticosteroids and beta-2 agonists. Family history is significant for colon cancer in her father. Blood pressure is 160/90 mm Hg and pulse is 80/min. On physical examination, there is symmetric proximal muscle weakness of the upper and lower extremities. Fasting plasma glucose level is 135 mg/dL and 24-hour urinary cortisol is increased. Further evaluation reveals that high-dose, but not low-dose, dexamethasone suppresses serum cortisol levels. Serum ACTH levels are high-normal. Which of the following is the most likely cause of this patient's symptoms?

- ✗ A. Adrenal adenoma (9%)
- B. Adrenal carcinoma (1%)
- C. Exogenous glucocorticoids (9%)
- ✓ D. Pituitary adenoma (70%)
- E. Small cell lung cancer (9%)

Incorrect
Correct answer
D

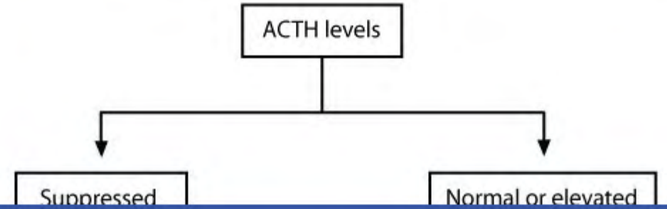
70%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

Diagnosing the cause of Cushing syndrome

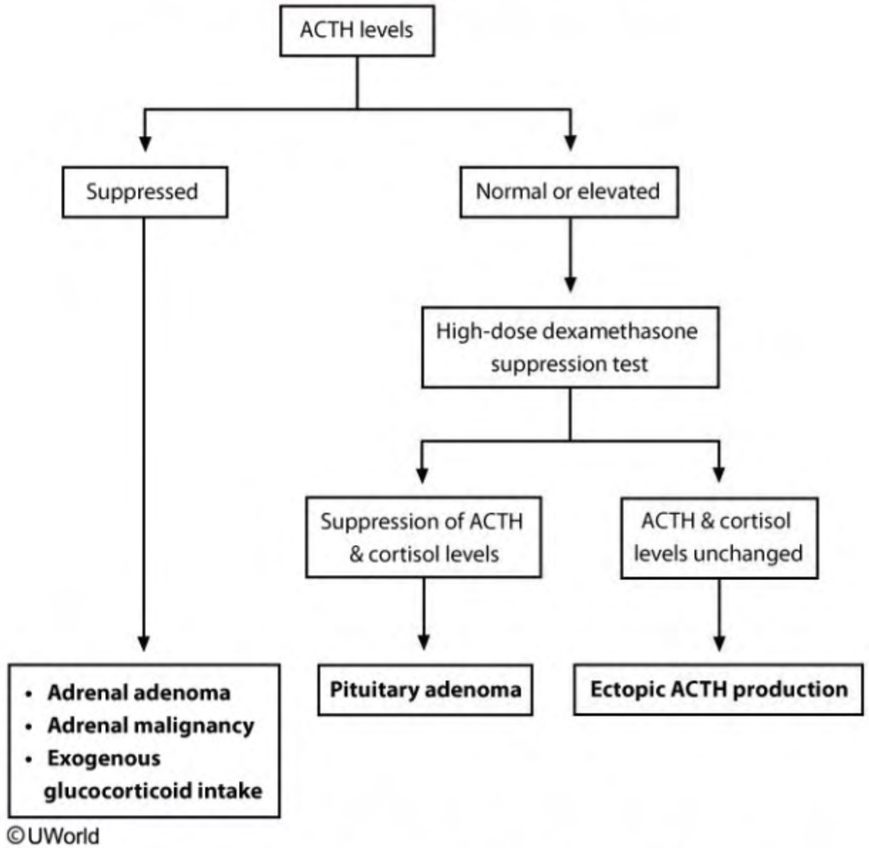


https://t.me/USMLEWorldStep1

A 56-year-old woman comes to the office due to progressive weight gain and fatigue over the last 4 months. She also h
bronch
colon
is sym
mg/dL
dexam
the mo

Exhibit Display

Diagnosing the cause of Cushing syndrome



©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Suppressed
Normal or elevated

https://t.me/USMLEWorldStep1

©UWorld

This patient has weight gain, proximal muscle weakness, hypertension, and hyperglycemia, which are prominent features of Cushing syndrome. Screening tests for endogenous Cushing syndrome include **low-dose dexamethasone suppression testing**. In normal individuals, low doses of dexamethasone (a potent glucocorticoid) suppress ACTH and cortisol levels through negative feedback. However, in endogenous Cushing syndrome, ACTH and cortisol levels are not suppressed.

The most common causes of Cushing syndrome are shown in the flowchart and can be categorized on the basis of serum ACTH levels as either ACTH dependent (ACTH is high or inappropriately normal) or ACTH independent (ACTH is suppressed). In ACTH-dependent Cushing syndrome, if **high-dose dexamethasone suppresses ACTH** and cortisol secretion, a **pituitary source** of ACTH (ie, ACTH-secreting pituitary adenoma) is likely. In contrast, ectopic ACTH production (eg, from malignant tumors such as small cell lung cancer) is not suppressed by high-dose dexamethasone **(Choice E)**.

This patient has excessive cortisol production that is suppressed by high-dose but not low-dose dexamethasone. This is consistent with an ACTH-secreting corticotroph pituitary adenoma (**Cushing disease**), the most common cause of endogenous Cushing syndrome.

(Choices A and B) Excess cortisol production due to an autonomously functioning adrenal adenoma, adrenal carcinoma, or primary adrenocortical hyperplasia will cause Cushing syndrome with a suppressed ACTH level (ACTH independent). This patient's ACTH is elevated.

(Choice C) Administration of exogenous glucocorticoids is a common cause of Cushing syndrome. This is most common with systemic agents (eg, prednisone), but can occasionally be seen with topical or inhaled glucocorticoids. However, ACTH is suppressed in these cases.

Educational objective:
In Cushing syndrome due to an ACTH-secreting pituitary adenoma (Cushing disease), ACTH is high and cortisol production can be suppressed by high-dose, but not low-dose, dexamethasone. In patients with ectopic ACTH production (eg, from malignant tumors), cortisol and ACTH production are not suppressed by low- or high-dose dexamethasone.

https://t.me/USMLEWorldStep1

©UWorld

This p
featur
dexan
glucoc
syndro

The m
serum
(ACTH

ACTH
contra
high-d

This p
This is
cause

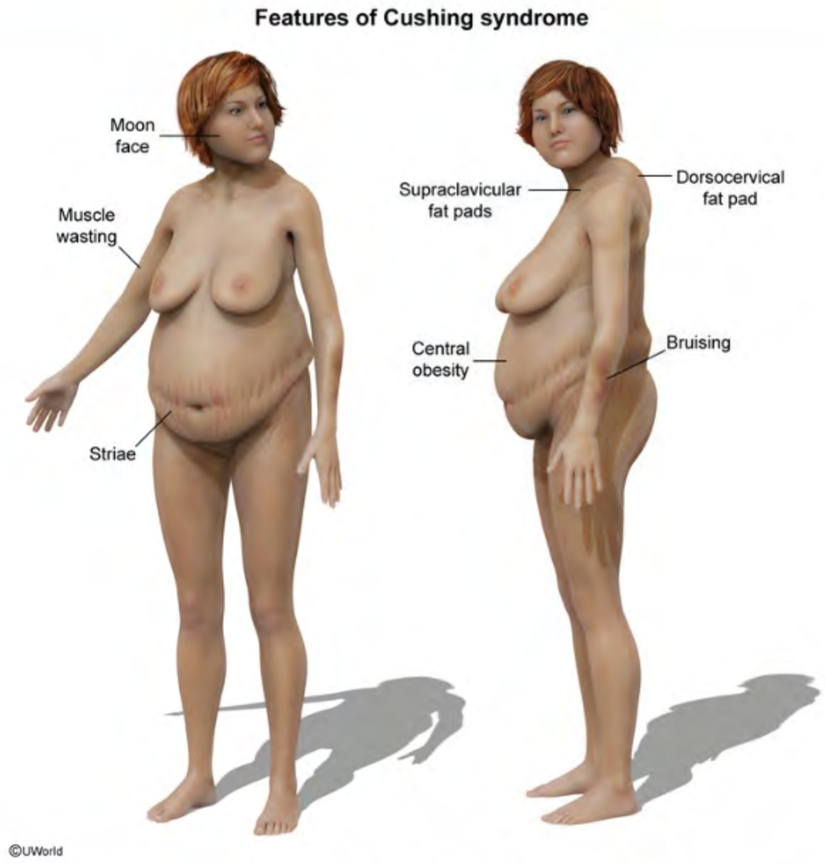
(Choi
carcin
(ACTH

(Choi
comm
glucoc

Educa
In Cus
produc
produc
dexamethasone.

Exhibit Display

Features of Cushing syndrome | Features of Cushing syndrome



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

©UWorld

This p
featur
dexan
glucoc
syndro

The m
serum
(ACTH
ACTH
contra
high-d

This p
This is
cause

(Choi
carcin
(ACTH

(Choi
comm
glucoc

Educa
In Cus
produc
produc
dexamethasone.

Exhibit Display

Features of Cushing syndrome | Features of Cushing syndrome

Features of Cushing syndrome	
Clinical manifestations	• **Central obesity** • Skin atrophy & wide, purplish **striae** • Proximal muscle weakness • Hypertension • **Glucose intolerance** • Skin hyperpigmentation (if due to ACTH excess) • Depression, anxiety
Diagnosis	• 24-hr urinary cortisol excretion • Late-night salivary cortisol assay • Low-dose dexamethasone suppression test

New | Existing | My Notebook

https://t.me/USMLEWorldStep1

A 5-year-old boy with developmental delay is brought to the office due to difficulty "seeing the board" at school. Examination shows a boy with a tall, thin habitus with elongated limbs. Funduscopy shows bilateral lens subluxation. Four years later, the patient dies suddenly of a massive cerebrovascular accident. Autopsy shows middle cerebral artery thrombosis and old renal infarcts. His parents wish to know if anything could have been done to have prevented his death. Which of the following would have been the most appropriate supplementation for this patient?

- A. Ascorbic acid
- B. Carnitine
- C. Pyridoxine
- D. Thiamine
- E. Tyrosine
- F. Vitamin K

Submit

https://t.me/USMLEWorldStep1

A 5-year-old boy with developmental delay is brought to the office due to difficulty "seeing the board" at school. Examination shows a boy with a tall, thin habitus with elongated limbs. Funduscopy shows bilateral lens subluxation. Four years later, the patient dies suddenly of a massive cerebrovascular accident. Autopsy shows middle cerebral artery thrombosis and old renal infarcts. His parents wish to know if anything could have been done to have prevented his death. Which of the following would have been the most appropriate supplementation for this patient?

- ✗ A. Ascorbic acid (31%)
- B. Carnitine (7%)
- ✓ C. Pyridoxine (39%)
- D. Thiamine (5%)
- E. Tyrosine (6%)
- F. Vitamin K (9%)

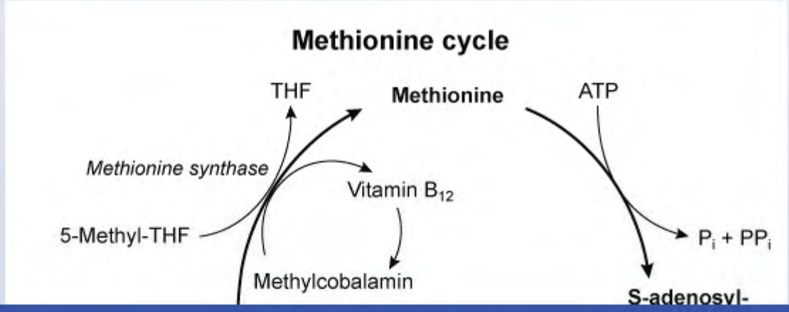
Incorrect
Correct answer
C

39%
Answered correctly

04 secs
Time Spent

2023
Version

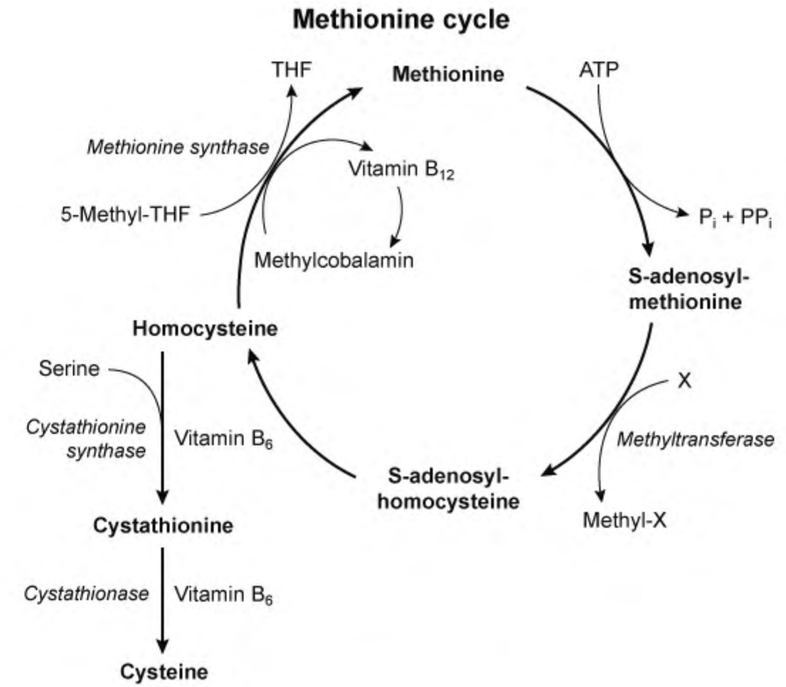
Explanation



https://t.me/USMLEWorldStep1

A 5-year-old boy with developmental delay is brought to the office due to difficulty "seeing the board" at school.
Exami
sublux
middle
done t
for this

Exhibit Display



P_i = inorganic phosphate; **PP_i** = inorganic pyrophosphate (diphosphate);
THF = tetrahydrofolate.

©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Methylcobalamin
S-adenosyl-

https://t.me/USMLEWorldStep1

This patient's presentation is most consistent with homocystinuria, the most common inborn error of methionine metabolism. Most patients present at age 3-10 with **ectopia lentis (dislocated lens)**. About half of patients have **intellectual disability**. Other clinical manifestations include a Marfanoid habitus (eg, elongated limbs, arachnodactyly, scoliosis). Patients are at high risk for **thromboembolic occlusion** of both large and small vessels, especially those of the brain, heart, and kidneys. Thromboembolic complications are the major cause of morbidity and mortality in these patients.

Homocystinuria is most frequently caused by an **autosomal recessive** deficiency of cystathionine beta-synthase, an enzyme that requires **pyridoxine (vitamin B6)** as a cofactor. Approximately 50% of affected patients respond to high doses of pyridoxine, which improves residual enzymatic activity and reduces plasma homocysteine levels. Additional treatment includes dietary **restriction of methionine**.

(Choice A) Vitamin C is a necessary cofactor for the hydroxylation of proline and lysine residues in collagen. Vitamin C deficiency results in decreased strength of collagen fibers and causes scurvy.

(Choice B) Carnitine assists with long-chain fatty acid transport into mitochondria. Deficiencies in carnitine (eg, primary systemic carnitine deficiency) lead to fatty acid oxidation defects in cardiac and skeletal muscle.

(Choice D) Thiamine (vitamin B1) deficiency can cause dry and wet beriberi and Wernicke-Korsakoff syndrome.

(Choice E) Tyrosine is a nonessential amino acid and the precursor for catecholamines such as dopamine, epinephrine, and norepinephrine.

(Choice F) Vitamin K is involved in the post-translational conversion of glutamate to gamma-carboxyglutamic acid. This modification is necessary for the function of many clotting factors and regulatory proteins involved in the coagulation cascade.

Educational objective:
Homocystinuria is most commonly caused by cystathionine synthase deficiency. Affected individuals have marfanoid habitus, ectopia lentis, and developmental delay. Significant morbidity and mortality are due primarily to thromboembolism. Many patients with homocystinuria respond dramatically to pyridoxine (vitamin B6) supplementation.

References

https://t.me/USMLEWorldStep1

This patient's presentation is most consistent with homocystinuria, the most common inborn error of methionine metab

intelle

arachn

vessel

morbi

Homo

an enz

to high

Additi

(Choi

Vitami

(Choi

primar

(Choi

(Choi

epinep

(Choi

acid.

coagu

Educa

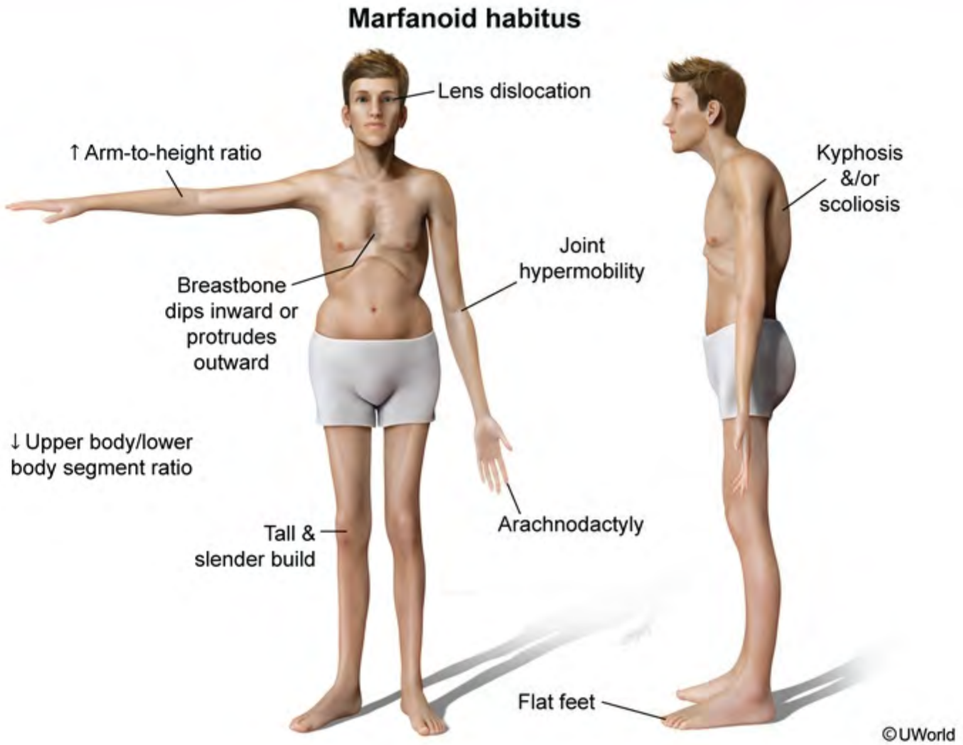
Homo

marfa

thromboembolism. Many patients with homocystinuria respond dramatically to pyridoxine (vitamin B6) supplementation.

References

Exhibit Display



Zoom In Zoom Out Reset New | Existing My Notebook

https://t.me/USMLEWorldStep1

This patient's presentation is most consistent with homocystinuria, the most common inborn error of methionine metabolism. Most patients present at age 3-10 with **ectopia lentis (dislocated lens)**. About half of patients have **intelle**
arachn
vessel
morbi

Homo
an enz
to high
Additi

(Choi
Vitami

(Choi
primar

(Choi

(Choi
epinep

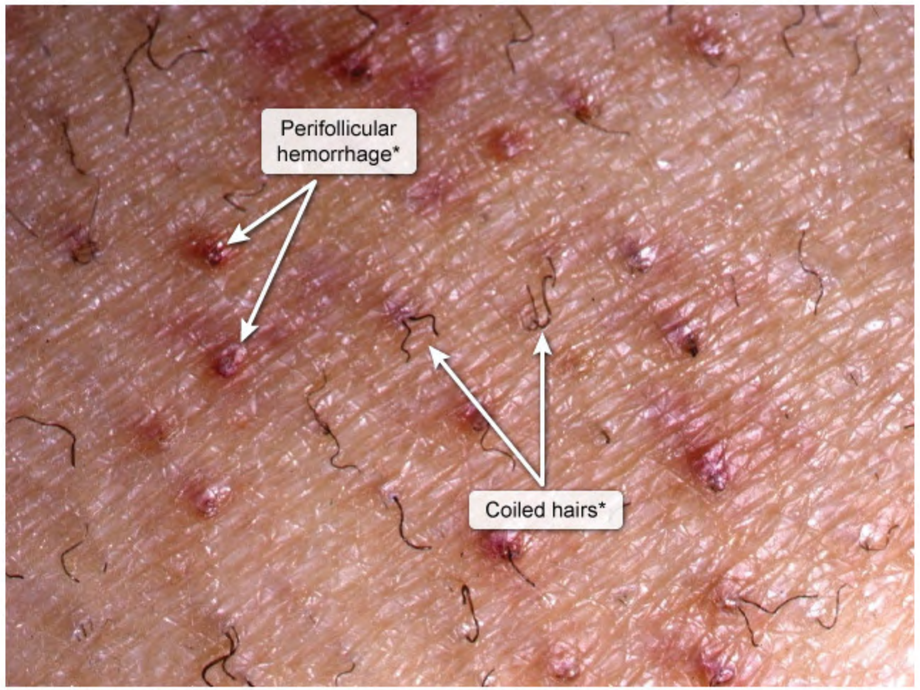
(Choi
acid.
coagu

Educa
Homo
marfa
thromb
supple

References

Exhibit Display

Vitamin C deficiency (scurvy)



*Due to impaired collagen formation.

©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

A 40-year-old man comes to the office due to recurrent epigastric abdominal pain, nausea, and watery diarrhea for the past several months. The patient has had similar burning pain previously and was treated for peptic ulcer disease. He has been taking over-the-counter antacids but with no significant symptom relief. The patient does not use tobacco, alcohol, or illicit drugs. Vital signs are within normal limits. Abdominal examination shows mild epigastric tenderness and increased bowel sounds. Testing for stool occult blood is positive, and laboratory studies show microcytic hypochromic anemia. Serum gastrin level is markedly elevated. Upper gastrointestinal endoscopy reveals prominent gastric folds and multiple ulcers in the duodenum and proximal jejunum. Given these findings, this patient should be assessed for a personal or family history of which of the following conditions?

- A. Cerebellar hemangioblastomas
- B. Mucosal neuromas
- C. Plexiform neurofibromas
- D. Recurrent nephrolithiasis
- E. Thyroid malignancy

Submit

https://t.me/USMLEWorldStep1

A 40-year-old man comes to the office due to recurrent epigastric abdominal pain, nausea, and watery diarrhea for the past several months. The patient has had similar burning pain previously and was treated for peptic ulcer disease. He has been taking over-the-counter antacids but with no significant symptom relief. The patient does not use tobacco, alcohol, or illicit drugs. Vital signs are within normal limits. Abdominal examination shows mild epigastric tenderness and increased bowel sounds. Testing for stool occult blood is positive, and laboratory studies show microcytic hypochromic anemia. Serum gastrin level is markedly elevated. Upper gastrointestinal endoscopy reveals prominent gastric folds and multiple ulcers in the duodenum and proximal jejunum. Given these findings, this patient should be assessed for a personal or family history of which of the following conditions?

- ✗ A. Cerebellar hemangioblastomas (5%)
- B. Mucosal neuromas (16%)
- C. Plexiform neurofibromas (7%)
- ✓ D. Recurrent nephrolithiasis (37%)
- E. Thyroid malignancy (33%)

Incorrect
Correct answer
D

37%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

Classification of multiple endocrine neoplasia	
Type 1	• **Primary hyperparathyroidism** (parathyroid adenomas or hyperplasia) • Pituitary tumors (prolactin, visual defects) • Pancreatic tumors (especially gastrinomas)

https://t.me/USMLEWorldStep1

Explanation

Classification of multiple endocrine neoplasia	
Type 1	• **Primary hyperparathyroidism** (parathyroid adenomas or hyperplasia) • Pituitary tumors (prolactin, visual defects) • Pancreatic tumors (especially gastrinomas)
Type 2A	• **Medullary thyroid cancer** (calcitonin) • Pheochromocytoma • Primary hyperparathyroidism (parathyroid hyperplasia)
Type 2B	• **Medullary thyroid cancer** (calcitonin) • Pheochromocytoma • Mucosal neuromas/marfanoid habitus

This patient's recurrent peptic ulcer disease, associated with chronic blood loss (iron deficiency) anemia and an elevated gastrin level, is likely due to a gastrin-secreting pancreatic tumor (**Zollinger-Ellison syndrome**). Although most gastrinomas are sporadic, 20%-30% occur in association with **multiple endocrine neoplasia type 1** (MEN1). This autosomal dominant disorder is most often due to mutations of the *MEN1* gene (menin protein) and is characterized by **p**arathyroid adenomas, **p**ituitary tumors, and **p**ancreatic endocrine tumors (the **3 Ps**).

Patients with Zollinger-Ellison syndrome or other pancreatic neuroendocrine tumors should be assessed for symptoms or family history of other MEN1 manifestations. Potential associated conditions include **primary hyperparathyroidism** (eg, hypercalcemia, constipation, **kidney stones**) and pituitary adenomas (eg, headaches, visual field defects).

(Choices A and C) Von Hippel-Lindau disease (VHL) is an autosomal dominant disorder characterized by multiple tumors, including hemangioblastomas, pheochromocytoma, and renal cell carcinoma. Plexiform neurofibromas are large aggregates of neuronal cells, supporting cells, and connective tissue that are seen in approximately 30%

https://t.me/USMLEWorldStep1

	• Pancreatic tumors (especially gastrinomas)
Type 2A	• **Medullary thyroid cancer** (calcitonin) • Pheochromocytoma • Primary hyperparathyroidism (parathyroid hyperplasia)
Type 2B	• **Medullary thyroid cancer** (calcitonin) • Pheochromocytoma • Mucosal neuromas/marfanoid habitus

This patient's recurrent peptic ulcer disease, associated with chronic blood loss (iron deficiency) anemia and an elevated gastrin level, is likely due to a gastrin-secreting pancreatic tumor (**Zollinger-Ellison syndrome**). Although most gastrinomas are sporadic, 20%-30% occur in association with **multiple endocrine neoplasia type 1** (MEN1). This autosomal dominant disorder is most often due to mutations of the *MEN1* gene (menin protein) and is characterized by **p**arathyroid adenomas, **p**ituitary tumors, and **p**ancreatic endocrine tumors (the **3 Ps**).

Patients with Zollinger-Ellison syndrome or other pancreatic neuroendocrine tumors should be assessed for symptoms or family history of other MEN1 manifestations. Potential associated conditions include **primary hyperparathyroidism** (eg, hypercalcemia, constipation, **kidney stones**) and pituitary adenomas (eg, headaches, visual field defects).

(Choices A and C) Von Hippel-Lindau disease (VHL) is an autosomal dominant disorder characterized by multiple tumors, including hemangioblastomas, pheochromocytoma, and renal cell carcinoma. Plexiform neurofibromas are large aggregates of neuronal cells, supporting cells, and connective tissue that are seen in approximately 30% of patients with neurofibromatosis type 1 (NF1). Although an increased incidence of pancreatic endocrine tumors has been reported in both VHL and NF1, these associations are much less frequent than in MEN1.

(Choices B and E) MEN2A consists of medullary thyroid cancer, pheochromocytoma, and primary hyperparathyroidism. MEN2B (also known as MEN3) is associated with medullary thyroid cancer, pheochromocytoma, mucosal neuromas, and a marfanoid habitus. The MEN2 syndromes are not associated with pancreatic endocrine tumors.

https://t.me/USMLEWorldStep1

Type 2B	• Pheochromocytoma • Mucosal neuromas/marfanoid habitus

This patient's recurrent peptic ulcer disease, associated with chronic blood loss (iron deficiency) anemia and an elevated gastrin level, is likely due to a gastrin-secreting pancreatic tumor (**Zollinger-Ellison syndrome**). Although most gastrinomas are sporadic, 20%-30% occur in association with **multiple endocrine neoplasia type 1** (MEN1). This autosomal dominant disorder is most often due to mutations of the *MEN1* gene (menin protein) and is characterized by **p**arathyroid adenomas, **p**ituitary tumors, and **p**ancreatic endocrine tumors (the **3 Ps**).

Patients with Zollinger-Ellison syndrome or other pancreatic neuroendocrine tumors should be assessed for symptoms or family history of other MEN1 manifestations. Potential associated conditions include **primary hyperparathyroidism** (eg, hypercalcemia, constipation, **kidney stones**) and pituitary adenomas (eg, headaches, visual field defects).

(Choices A and C) Von Hippel-Lindau disease (VHL) is an autosomal dominant disorder characterized by multiple tumors, including hemangioblastomas, pheochromocytoma, and renal cell carcinoma. Plexiform neurofibromas are large aggregates of neuronal cells, supporting cells, and connective tissue that are seen in approximately 30% of patients with neurofibromatosis type 1 (NF1). Although an increased incidence of pancreatic endocrine tumors has been reported in both VHL and NF1, these associations are much less frequent than in MEN1.

(Choices B and E) MEN2A consists of medullary thyroid cancer, pheochromocytoma, and primary hyperparathyroidism. MEN2B (also known as MEN3) is associated with medullary thyroid cancer, pheochromocytoma, mucosal neuromas, and a marfanoid habitus. The MEN2 syndromes are not associated with pancreatic endocrine tumors.

Educational objective:
Multiple endocrine neoplasia type 1 consists of hyperparathyroidism (eg, hypercalcemia, constipation, kidney stones), pituitary tumors, and pancreatic endocrine tumors (eg, gastrinoma). The genetic defect involves mutations of the *MEN1* gene.

References

- Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1).

https://t.me/USMLEWorldStep1

A 50-year-old man comes to the office following transsphenoidal resection of a growth hormone–secreting pituitary adenoma. Three months ago, the patient was diagnosed with acromegaly. MRI of the pituitary showed a 14-mm sellar mass pressing on the optic chiasm and extending into the right cavernous sinus. The surgeon was able to only partially resect the pituitary mass because of the extension into the right cavernous sinus. Medical therapy for acromegaly with octreotide is planned. Which of the following changes are likely to occur following octreotide treatment in this patient?

	Adenoma size	Growth hormone level	Insulin-like growth factor-1 level
○ A.	↓	↓	↓
○ B.	↑	↑	↓
○ C.	↑	↑	↑
○ D.	No change	↑	↓
○ E.	↑	↓	↓

Submit

https://t.me/USMLEWorldStep1

A 50-year-old man comes to the office following transsphenoidal resection of a growth hormone–secreting pituitary adenoma. Three months ago, the patient was diagnosed with acromegaly. MRI of the pituitary showed a 14-mm sellar mass pressing on the optic chiasm and extending into the right cavernous sinus. The surgeon was able to only partially resect the pituitary mass because of the extension into the right cavernous sinus. Medical therapy for acromegaly with octreotide is planned. Which of the following changes are likely to occur following octreotide treatment in this patient?

	Adenoma size	Growth hormone level	Insulin-like growth factor-1 level	
✓ A.	↓	↓	↓	(80%)
✗ B.	↑	↑	↓	(3%)
C.	↑	↑	↑	(1%)
D.	No change	↑	↓	(7%)
E.	↑	↓	↓	(7%)

Incorrect
Correct answer
A

80%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

Acromegaly is characterized by the **excessive secretion of growth hormone** (GH), usually due to a somatotroph **pituitary adenoma**. The actions of GH are mediated primarily by **insulin-like growth factor-1** (IGF-1) from the liver; classic manifestations include bony enlargement of the hands and skull (eg, frontal bossing, jaw malocclusion), arthropathy, cardiomyopathy, and skin thickening. In most cases, initial treatment includes transsphenoidal resection of the tumor. However, if the tumor is unresectable or incompletely resected, the phenotypic manifestations may progress. For these patients, additional medical therapy is indicated.

https://t.me/USMLEWorldStep1

Explanation

Acromegaly is characterized by the **excessive secretion of growth hormone** (GH), usually due to a somatotroph **pituitary adenoma**. The actions of GH are mediated primarily by **insulin-like growth factor-1** (IGF-1) from the liver; classic manifestations include bony enlargement of the hands and skull (eg, frontal bossing, jaw malocclusion), arthropathy, cardiomyopathy, and skin thickening. In most cases, initial treatment includes transsphenoidal resection of the tumor. However, if the tumor is unresectable or incompletely resected, the phenotypic manifestations may progress. For these patients, additional medical therapy is indicated.

Octreotide is a long-acting octapeptide **somatostatin analogue** that has an altered amino acid sequence in the non–receptor binding domain, which makes it more resistant to degradation than native somatostatin. Like somatostatin, octreotide has a broad range of antisecretory actions mediated by membrane receptors. In patients with acromegaly, it inhibits GH secretion and subsequently **reduces IGF-1 release**, which can mitigate many of the clinical manifestations of the disease. It also exerts an anti-proliferative effect on somatotroph cells and helps **reduce residual adenoma size** in many patients **(Choice E)**.

(Choices B and D) Pegvisomant is a competitive inhibitor of GH that blocks the binding of GH to its receptor. This drug reduces GH-induced IGF-1 secretion and the subsequent downstream effects but does not alter GH secretion. Adenoma size may remain stable or increase somewhat.

(Choice C) Medical treatment (eg, octreotide) is indicated for patients with incompletely resected somatotroph adenomas because, without treatment, the residual tissue will likely continue to grow and secrete GH, inducing a rise in IGF-1 levels.

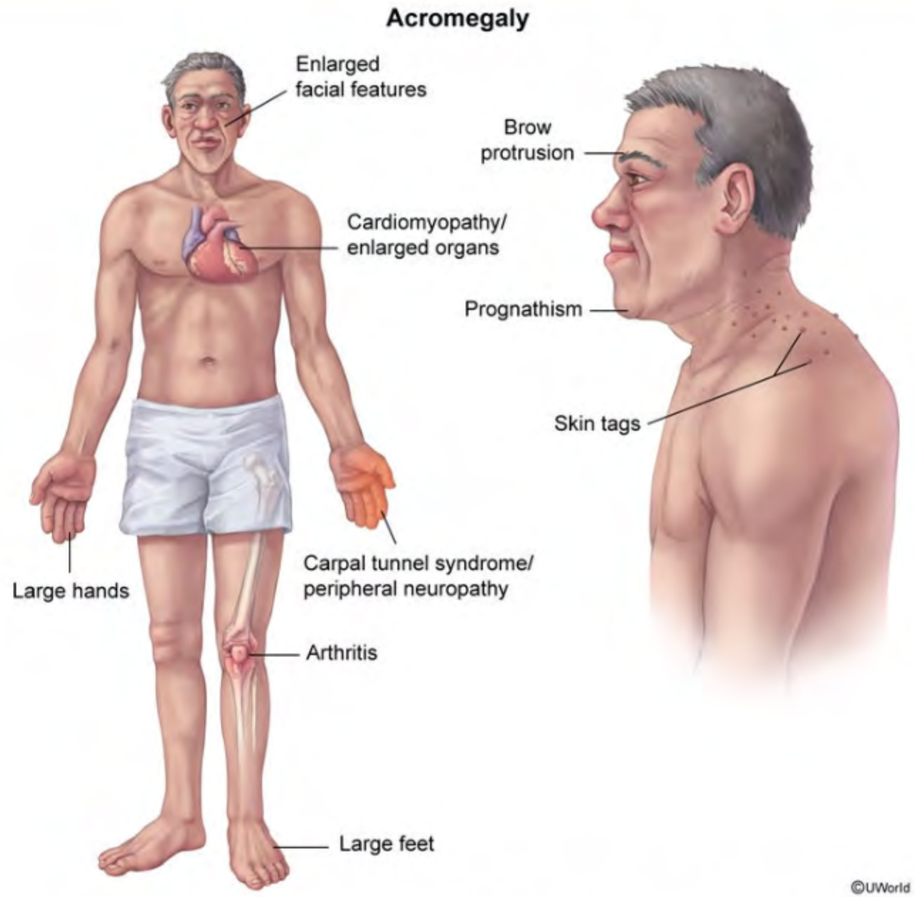
Educational objective:
Acromegaly is usually treated with resection of the somatotroph pituitary adenoma, but additional medical therapy is needed for patients with residual tumor. Octreotide is a long-acting somatostatin analogue that inhibits growth hormone secretion and, subsequently, insulin-like growth factor-1 release. It also reduces residual adenoma size in many patients.

Pharmacology Endocrine, Diabetes & Metabolism Acromegaly

https://t.me/USMLEWorldStep1

Explanation

Exhibit Display



Zoom In Zoom Out Reset New | Existing My Notebook

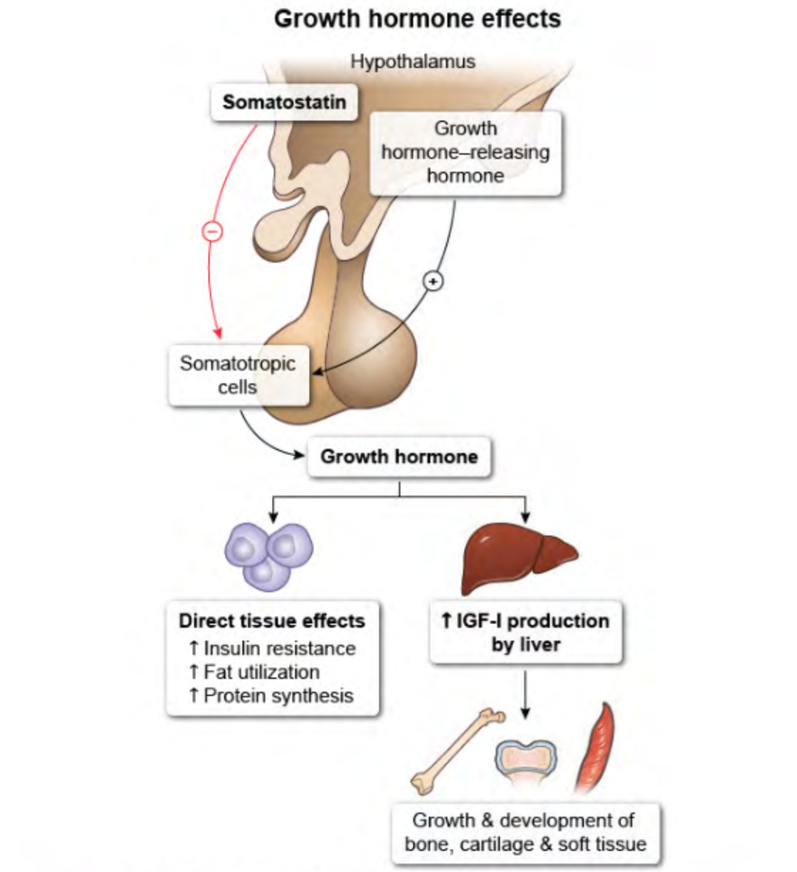
Acron
somat
1) fron
maloc
transs
pheno
Octre
non–re
somat
with a
clinica
reduc
(Choi
drug re
secret
(Choi
adeno
rise in
Educa
Acrom
is nee
hormo
in mar

Pharmacology Endocrine, Diabetes & Metabolism Acromegaly

https://t.me/USMLEWorldStep1

Explanation

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Pharmacology | Endocrine, Diabetes & Metabolism | Acromegaly

https://t.me/USMLEWorldStep1

A newborn boy is found to have markedly elevated serum TSH and low thyroxine on routine screening. Laboratory findings using a venous blood sample confirm the diagnosis. The patient was born at 39 weeks gestation to a 34-year-old healthy woman, who had been taking prenatal vitamins regularly. He has no symptoms or abnormal findings on clinical examination. Imaging studies reveal an ectopic thyroid gland just below the tongue. Which of the following is the most likely cause of this patient's otherwise normal physical examination despite abnormal thyroid laboratory findings?

- A. Excess thyroxine production by an ectopic thyroid
- B. Increased thyroid-binding globulin in pregnancy
- C. Transplacental transfer of thyroid-stimulating antibody
- D. Transplacental transfer of thyroxine
- E. Transplacental transfer of TSH

Submit

https://t.me/USMLEWorldStep1

A newborn boy is found to have markedly elevated serum TSH and low thyroxine on routine screening. Laboratory findings using a venous blood sample confirm the diagnosis. The patient was born at 39 weeks gestation to a 34-year-old healthy woman, who had been taking prenatal vitamins regularly. He has no symptoms or abnormal findings on clinical examination. Imaging studies reveal an ectopic thyroid gland just below the tongue. Which of the following is the most likely cause of this patient's otherwise normal physical examination despite abnormal thyroid laboratory findings?

- A. Excess thyroxine production by an ectopic thyroid (12%)
- ✗ B. Increased thyroid-binding globulin in pregnancy (19%)
- C. Transplacental transfer of thyroid-stimulating antibody (6%)
- ✓ D. Transplacental transfer of thyroxine (53%)
- E. Transplacental transfer of TSH (7%)

Incorrect
Correct answer
D

53%
Answered correctly

05 secs
Time Spent

2023
Version

Explanation

Congenital hypothyroidism	
Clinical manifestations	• Asymptomatic at birth • After maternal thyroxine wanes (weeks to months): ◦ Lethargy, poor feeding ◦ Enlarged fontanelle ◦ Protruding tongue, puffy face, umbilical hernia ◦ Constipation ◦ Prolonged jaundice

https://t.me/USMLEWorldStep1

Congenital hypothyroidism	
Clinical manifestations	• Asymptomatic at birth • After maternal thyroxine wanes (weeks to months): ◦ Lethargy, poor feeding ◦ Enlarged fontanelle ◦ Protruding tongue, puffy face, umbilical hernia ◦ Constipation ◦ Prolonged jaundice ◦ Dry skin
Diagnosis	• ↑ TSH & ↓ free thyroxine levels • Newborn screening
Treatment	• Levothyroxine*
*Delayed treatment is associated with neurocognitive dysfunction (eg, ↓ intelligence quotient).	

This infant has **primary hypothyroidism**, a congenital disorder that is most commonly caused by abnormal thyroid gland development (ie, agenesis, hypoplasia) or location (ectopy). During normal embryogenesis, the thyroid descends from the developing pharynx to its normal location anterior to the trachea. Abnormal migration results in an **ectopic thyroid** (eg, lingual, mediastinal), as seen in this patient.

Most patients with thyroid dysgenesis have hypothyroidism, with routine newborn screening findings of increased TSH and decreased thyroxine (T4) levels. However, **newborns** are typically **asymptomatic** for the first weeks due to the presence of **maternal T4**, which **crosses the placenta in small amounts** during gestation. The amount of neonatal **T4 is still low** compared to that in unaffected patients but is sufficient to initially prevent clinical manifestations of hypothyroidism.

As maternally derived neonatal T4 begins to wane in the first few weeks to months of life, classic symptoms of untreated hypothyroidism develop. Presenting signs include lethargy, hypotonia, constipation, and poor feeding. A hoarse cry, macroglossia, facial edema, and prolonged jaundice are also common.

https://t.me/USMLEWorldStep1

*Delayed treatment is associated with neurocognitive dysfunction (eg, ↓ intelligence quotient).

This infant has **primary hypothyroidism**, a congenital disorder that is most commonly caused by abnormal thyroid gland development (ie, agenesis, hypoplasia) or location (ectopy). During normal embryogenesis, the thyroid descends from the developing pharynx to its normal location anterior to the trachea. Abnormal migration results in an **ectopic thyroid** (eg, lingual, mediastinal), as seen in this patient.

Most patients with thyroid dysgenesis have hypothyroidism, with routine newborn screening findings of increased TSH and decreased thyroxine (T4) levels. However, **newborns** are typically **asymptomatic** for the first weeks due to the presence of **maternal T4**, which **crosses the placenta in small amounts** during gestation. The amount of neonatal **T4 is still low** compared to that in unaffected patients but is sufficient to initially prevent clinical manifestations of hypothyroidism.

As maternally derived neonatal T4 begins to wane in the first few weeks to months of life, classic symptoms of untreated hypothyroidism develop. Presenting signs include lethargy, hypotonia, constipation, and poor feeding. A hoarse cry, macroglossia, facial edema, and prolonged jaundice are also common.

(Choice A) Ectopic thyroid tissue typically produces decreased, not increased, T4.

(Choice B) Physiologically increased thyroid-binding globulin (TBG) levels in pregnancy result in increased total maternal T4 and triiodothyronine (T3) to maintain a euthyroid state. Because maternal levels of free T4 and T3 remain normal, the increase in maternal TBG does not affect the fetus.

(Choice C) Transplacental transfer of thyroid-stimulating antibodies in mothers with Graves disease results in transient neonatal hyperthyroidism (neonatal Graves disease). Laboratory findings would show increased T4 and decreased TSH.

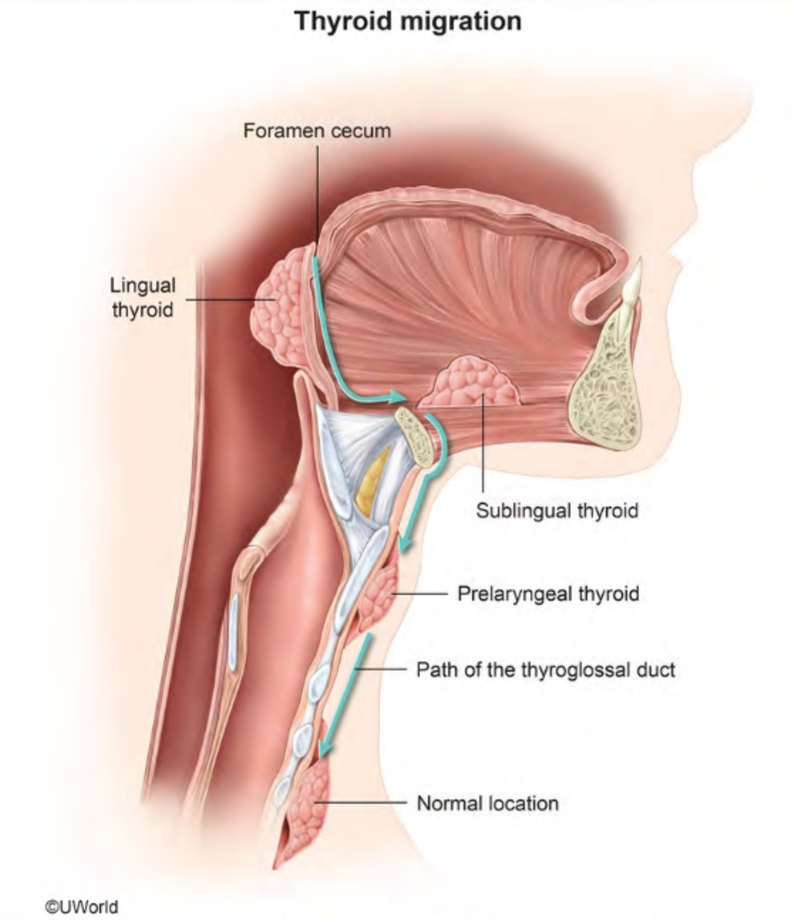
(Choice E) TSH is a polypeptide hormone that does not cross the placenta.

Educational objective:
Congenital hypothyroidism, most commonly caused by abnormal thyroid gland development or location (ie, ectopy), is identified by elevated TSH and decreased thyroxine (T4) levels. Clinical manifestations of hypothyroidism are not present at birth due to the transplacental transfer of small amounts of maternal T4.

https://t.me/USMLEWorldStep1

*Delayed treatment is associated with neurocognitive dysfunction (eg, ↓ intelligence quotient).

Exhibit Display



Zoom In Zoom Out Reset New | Existing My Notebook

This ir
gland
desce
an **ect**

Most p
TSH a
to the
neona
manife

As ma
untrea
hoarse

(Choi

(Choi
matern
remain

(Choi
transie
decrea

(Choi

Educa
Conge
ectopy), is identified by elevated TSH and decreased thyroxine (T4) levels. Clinical manifestations of hypothyroidism are not present at birth due to the transplacental transfer of small amounts of maternal T4.

https://t.me/USMLEWorldStep1

A 76-year-old woman is brought to the hospital after her daughter found her unresponsive in the morning. The patient and her daughter walked extensively during a family outing the previous day; the patient then skipped dinner and went to bed as soon as they returned home. Medical history includes type 2 diabetes mellitus managed with an oral medication. Blood pressure is 140/80 mm Hg and pulse is 102/min. The patient is diaphoretic and responds only to pain. Blood glucose is 34 mg/dL. Her condition rapidly improves after administration of an intravenous bolus of dextrose, but she becomes confused again several hours later. Repeat blood glucose is 39 mg/dL. Which of the following medications is the most likely cause of this patient's current condition?

- A. Acarbose
- B. Glyburide
- C. Metformin
- D. Pioglitazone
- E. Sitagliptin

Submit

https://t.me/USMLEWorldStep1

A 76-year-old woman is brought to the hospital after her daughter found her unresponsive in the morning. The patient and her daughter walked extensively during a family outing the previous day; the patient then skipped dinner and went to bed as soon as they returned home. Medical history includes type 2 diabetes mellitus managed with an oral medication. Blood pressure is 140/80 mm Hg and pulse is 102/min. The patient is diaphoretic and responds only to pain. Blood glucose is 34 mg/dL. Her condition rapidly improves after administration of an intravenous bolus of dextrose, but she becomes confused again several hours later. Repeat blood glucose is 39 mg/dL. Which of the following medications is the most likely cause of this patient's current condition?

- ✗ A. Acarbose (4%)
- ✓ B. Glyburide (64%)
- C. Metformin (10%)
- D. Pioglitazone (9%)
- E. Sitagliptin (10%)

Incorrect
Correct answer
B

64%
Answered correctly

05 secs
Time Spent

2023
Version

Explanation

Noninsulin antidiabetic agents for type 2 diabetes mellitus		
Agent	**Mechanism of action**	**Adverse effects**
Insulin secretagogues • Sulfonylureas • Meglitinides	↑ Insulin secretion by inhibiting β-cell K_{ATP} channels	• Hypoglycemia • Weight gain
	Stimulate AMPK & inhibit mitochondrial	

https://t.me/USMLEWorldStep1

Noninsulin antidiabetic agents for type 2 diabetes mellitus		
Agent	**Mechanism of action**	**Adverse effects**
Insulin secretagogues • Sulfonylureas • Meglitinides	↑ Insulin secretion by inhibiting β-cell K_{ATP} channels	• Hypoglycemia • Weight gain
Biguanides • Metformin	Stimulate AMPK & inhibit mitochondrial gluconeogenesis, ↓ hepatic glucose production & ↑ peripheral glucose uptake	• Diarrhea • Lactic acidosis
Thiazolidinediones • Pioglitazone	Activate transcription regulator PPAR-γ, ↓ insulin resistance	• Fluid retention/heart failure • Weight gain
GLP-1 agonists • Exenatide • Liraglutide	↑ Glucose-dependent insulin secretion, ↓ glucagon secretion, delayed gastric emptying	• Pancreatitis • Weight loss
DPP4 inhibitors • Sitagliptin • Saxagliptin	↑ Endogenous GLP-1 & GIP levels	• Nasopharyngitis
SGLT-2 inhibitors • Canagliflozin • Dapagliflozin	↑ Renal glucose excretion	• Urinary tract infections • Hypotension

AMPK = AMP-activated protein kinase; **DPP4** = dipeptidyl peptidase-4; **GIP** = gastric inhibitory polypeptide; **GLP-1** = glucagon-like peptide-1; **K_{ATP}** = ATP-sensitive potassium; **PPAR-γ** = peroxisome proliferator–activated receptor γ; **SGLT-2** = sodium-glucose cotransporter-2.

This patient's **persistent hypoglycemia** indicates **excessive insulin secretion** caused by her diabetes medication, which is most likely a **sulfonylurea** (eg, glyburide, glimepiride). Sulfonylureas bind to a receptor on

https://t.me/USMLEWorldStep1

This patient's **persistent hypoglycemia** indicates **excessive insulin secretion** caused by her diabetes medication, which is most likely a **sulfonylurea** (eg, glyburide, glimepiride). Sulfonylureas bind to a receptor on pancreatic beta cells and inhibit the ATP-sensitive potassium channel, altering the cell's resting potential and resulting in calcium influx stimulating exocytosis of insulin secretory granules. The increased insulin secretion occurs **independent of blood glucose** concentrations (ie, even when blood glucose concentrations are low).

Hypoglycemia with sulfonylureas can be induced by exercise, missed meals, or initiation of additional antidiabetic medications. The risk is greater in the elderly population and in patients with chronic kidney disease or hepatic impairment (due to slower drug metabolism and clearance). The hypoglycemia may reoccur following successful initial treatment until the drug has been fully cleared.

(Choice A) Acarbose is an alpha-glucosidase inhibitor that decreases intestinal carbohydrate digestion and glucose absorption, thereby blunting postprandial hyperglycemia. It is not associated with hypoglycemia because the medication does not induce insulin secretion.

(Choice C) Metformin is a biguanide that decreases hepatic gluconeogenesis and intestinal glucose absorption and increases peripheral glucose uptake and use. Because metformin does not increase endogenous insulin production, it is not associated with hypoglycemia.

(Choice D) Thiazolidinediones (eg, pioglitazone) increase insulin sensitivity by increasing glucose use and decreasing glucose production in adipose tissue, muscle, and liver. Thiazolidinediones do not increase endogenous insulin production and therefore carry a low risk of hypoglycemia.

(Choice E) Unlike sulfonylureas, dipeptidyl peptidase-4 inhibitors (eg, sitagliptin) and glucagon-like peptide-1 agonists (eg, exenatide) increase *glucose-dependent* insulin release from the pancreatic beta cells. The effects on insulin release diminish as glucose levels approach normal (eg, fasting state), and therefore, hypoglycemia risk is very low.

Educational objective:
Sulfonylureas (eg, glyburide, glimepiride) increase insulin secretion by pancreatic beta cells independent of blood glucose concentration. These medications have a high incidence of hypoglycemia, especially in the elderly population.

https://t.me/USMLEWorldStep1

A 57-year-old woman comes to the office due to left breast pain associated with fatigue, nausea, and unexplained weight loss. She is referred for mammography, which reveals a 3-cm dominant mass in the left breast. Biopsy confirms the mass to be adenocarcinoma, and subsequent studies find that the tumor is estrogen receptor-positive and human epidermal growth factor receptor 2- (HER2) negative. The patient experienced menopause at age 52, and her past medical history is otherwise unremarkable. Anastrozole treatment is initiated and leads to a substantial decrease in the size of the primary tumor. Which of the following is the best explanation for the therapeutic effect of this agent?

- A. Decreased androgen aromatization
- B. Decreased androgen synthesis
- C. Decreased follicular cell stimulation
- D. Impaired ligand-receptor interaction
- E. Impaired second-messenger action

Submit

https://t.me/USMLEWorldStep1

A 57-year-old woman comes to the office due to left breast pain associated with fatigue, nausea, and unexplained weight loss. She is referred for mammography, which reveals a 3-cm dominant mass in the left breast. Biopsy confirms the mass to be adenocarcinoma, and subsequent studies find that the tumor is estrogen receptor-positive and human epidermal growth factor receptor 2- (HER2) negative. The patient experienced menopause at age 52, and her past medical history is otherwise unremarkable. Anastrozole treatment is initiated and leads to a substantial decrease in the size of the primary tumor. Which of the following is the best explanation for the therapeutic effect of this agent?

- ✓ A. Decreased androgen aromatization (70%)
- B. Decreased androgen synthesis (9%)
- C. Decreased follicular cell stimulation (3%)
- D. Impaired ligand-receptor interaction (14%)
- E. Impaired second-messenger action (2%)

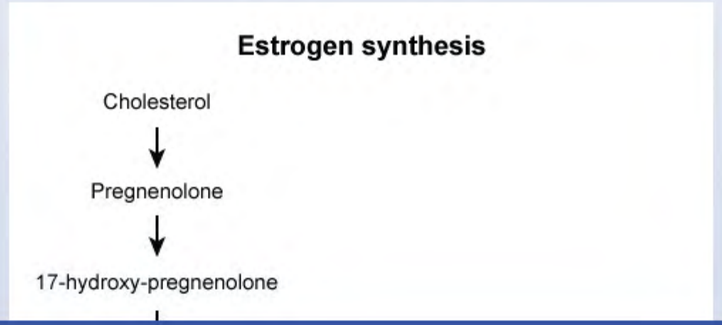
Correct

70%
Answered correctly

04 secs
Time Spent

2023
Version

Explanation

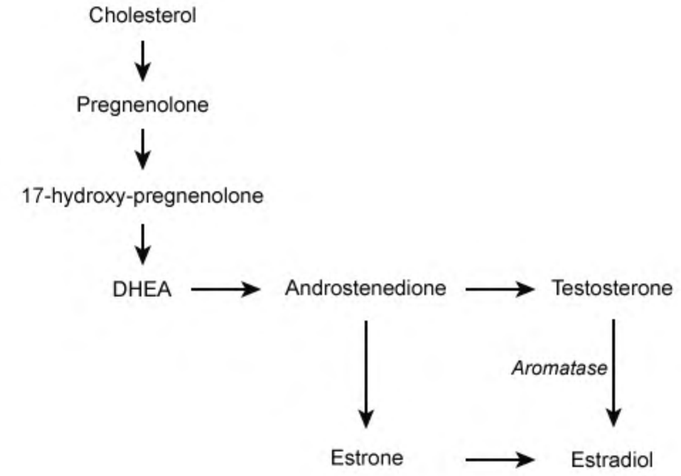


https://t.me/USMLEWorldStep1

A 57-year-old woman comes to the office due to left breast pain associated with fatigue, nausea, and unexplained weight
confirm
and hu
and he
substa
therap

Exhibit Display

Estrogen synthesis



DHEA = dehydroepiandrosterone.

©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

17-hydroxy-pregnenolone

https://t.me/USMLEWorldStep1



DHEA = dehydroepiandrosterone.

©UWorld

Estrogens are synthesized primarily by the aromatization of androgens. **Aromatase** belongs to the P450 superfamily and is highly expressed in **ovarian tissue** (in which expression is **gonadotropin dependent**). Aromatase is also expressed in the adrenal cortex, subcutaneous fat, and breast. In the postmenopausal state, follicular atresia leads to reduced numbers of granulosa cells and decreased ovarian estrogen synthesis. However, the ovaries and adrenal glands continue to produce androgens in significant quantities, and **extraovarian aromatase** maintains a low level of estrogen in the peripheral circulation.

Estrogen is the main hormone driving the growth and development of estrogen receptor (ER)-positive malignant breast tumors. **Aromatase inhibitors** (eg, anastrozole, letrozole, exemestane) reduce the synthesis of estrogen from androgens, suppressing estrogen levels in postmenopausal women and **slowing progression of ER-positive tumors**. They are less effective as monotherapy in premenopausal women, as ovarian aromatase is upregulated substantially in response to gonadotropins.

(Choice B) Although inhibition of androgen synthesis could theoretically decrease estrogen synthesis, most androgen synthesis inhibitors (eg, ketoconazole) are nonspecific and suppress other pathways of steroidogenesis (eg, cortisol, mineralocorticoid).

(Choice C) Pulsatile stimulation of the pituitary by gonadotropin-releasing hormone (GnRH) increases secretion of LH and FSH. However, continuous GnRH stimulation by long-acting GnRH analogs (eg, goserelin) suppresses LH and FSH release, decreasing production of estrogens in the ovarian follicle. These agents are useful for ovarian suppression in premenopausal women with ER-positive breast cancer.

(Choice D) Tamoxifen acts as either an antagonist or a partial agonist of the estrogen receptor, depending on the tissue. In breast tissue, tamoxifen antagonizes the estrogen receptor and can be used as adjuvant therapy for ER-positive breast cancer.

(Choice E) Many breast cancers overexpress epidermal growth factor receptor 2 (HER2). Trastuzumab is a monoclonal antibody against HER2 that is used in patients with HER2-positive tumors. It inhibits MAPK and PI3K/Akt signaling pathways, increases degradation of HER2, and facilitates antibody-mediated destruction of

https://t.me/USMLEWorldStep1

However, the ovaries and adrenal glands continue to produce androgens in significant quantities, and **extraovarian aromatase** maintains a low level of estrogen in the peripheral circulation.

Estrogen is the main hormone driving the growth and development of estrogen receptor (ER)-positive malignant breast tumors. **Aromatase inhibitors** (eg, anastrozole, letrozole, exemestane) reduce the synthesis of estrogen from androgens, suppressing estrogen levels in postmenopausal women and **slowing progression of ER-positive tumors**. They are less effective as monotherapy in premenopausal women, as ovarian aromatase is upregulated substantially in response to gonadotropins.

(Choice B) Although inhibition of androgen synthesis could theoretically decrease estrogen synthesis, most androgen synthesis inhibitors (eg, ketoconazole) are nonspecific and suppress other pathways of steroidogenesis (eg, cortisol, mineralocorticoid).

(Choice C) Pulsatile stimulation of the pituitary by gonadotropin-releasing hormone (GnRH) increases secretion of LH and FSH. However, continuous GnRH stimulation by long-acting GnRH analogs (eg, goserelin) suppresses LH and FSH release, decreasing production of estrogens in the ovarian follicle. These agents are useful for ovarian suppression in premenopausal women with ER-positive breast cancer.

(Choice D) Tamoxifen acts as either an antagonist or a partial agonist of the estrogen receptor, depending on the tissue. In breast tissue, tamoxifen antagonizes the estrogen receptor and can be used as adjuvant therapy for ER-positive breast cancer.

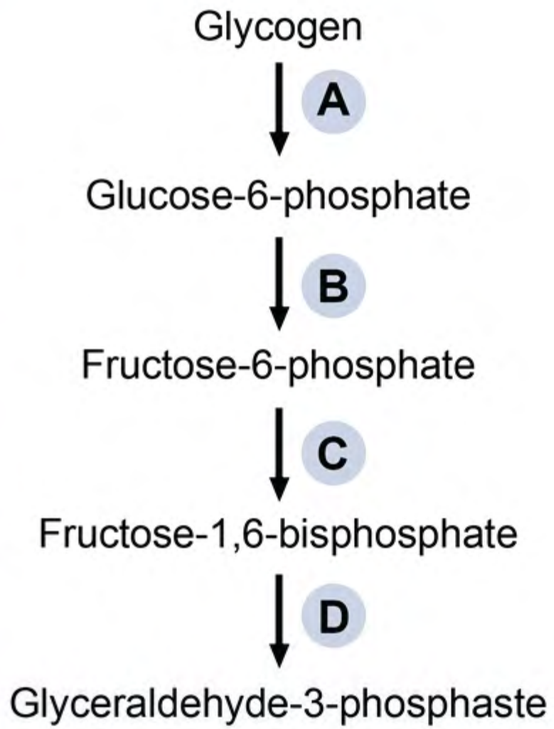
(Choice E) Many breast cancers overexpress epidermal growth factor receptor 2 (HER2). Trastuzumab is a monoclonal antibody against HER2 that is used in patients with HER2-positive tumors. It inhibits MAPK and PI3K/Akt signaling pathways, increases degradation of HER2, and facilitates antibody-mediated destruction of tumor cells.

Educational objective:
Estrogen is the main hormone responsible for the growth and development of estrogen receptor (ER)-positive breast tumors. Aromatase inhibitors (eg, anastrozole, letrozole, exemestane) decrease the synthesis of estrogen from androgens, suppressing estrogen levels and slowing progression of ER-positive tumors.

References

https://t.me/USMLEWorldStep1

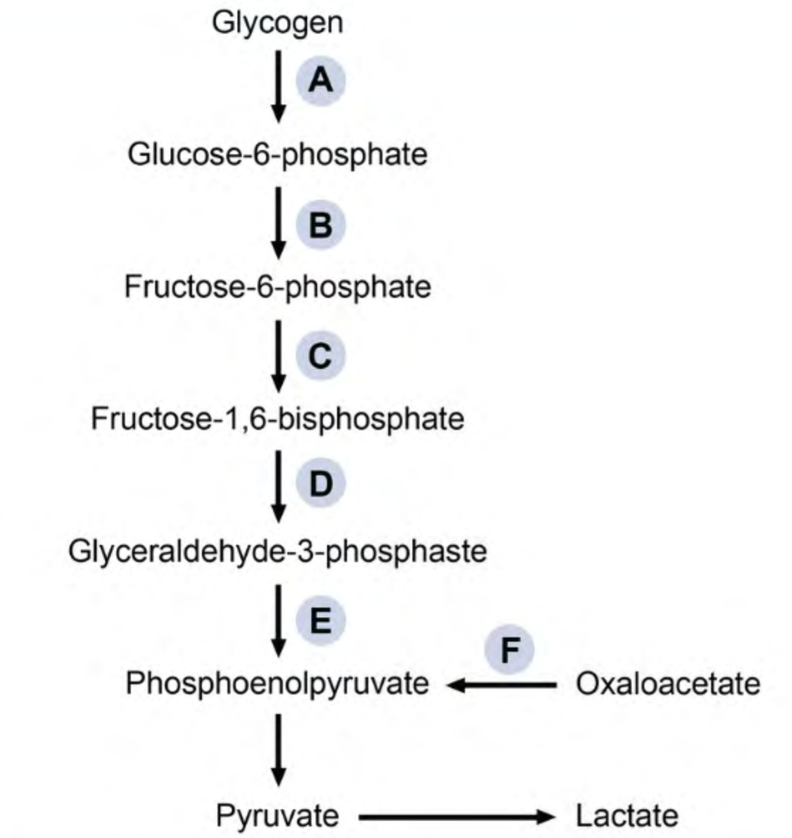
A 34-year-old woman is brought to the emergency department in the early morning with confusion, tremor, and sweating. Her husband reports that she did not wake to her alarm clock and was difficult to arouse. Over the past week, the patient has had similar episodes in the morning before eating and after exercise. Past medical history is unremarkable. Blood pressure is 135/95 mm Hg, pulse is 110/min, and respirations are 24/min. The patient is arousable to voice but does not follow commands. Cranial nerve examination, muscle tone, and deep tendon reflexes are normal. A bedside fingerstick glucose level is 35 mg/dL. The patient is given an intravenous infusion of glucose, which rapidly improves her mental status. Further evaluation reveals that her episodes of hypoglycemia are due to increased levels of an endogenous hormone. This hormonal imbalance is most likely causing the patient's symptoms by stimulating which of the following conversions?



https://t.me/USMLEWorldStep1

A 34-year-old woman is brought to the emergency department in the early morning with confusion, tremor, and sweati
week,
unrem
arousa
reflexe
of gluc
hypog
causin

Exhibit Display

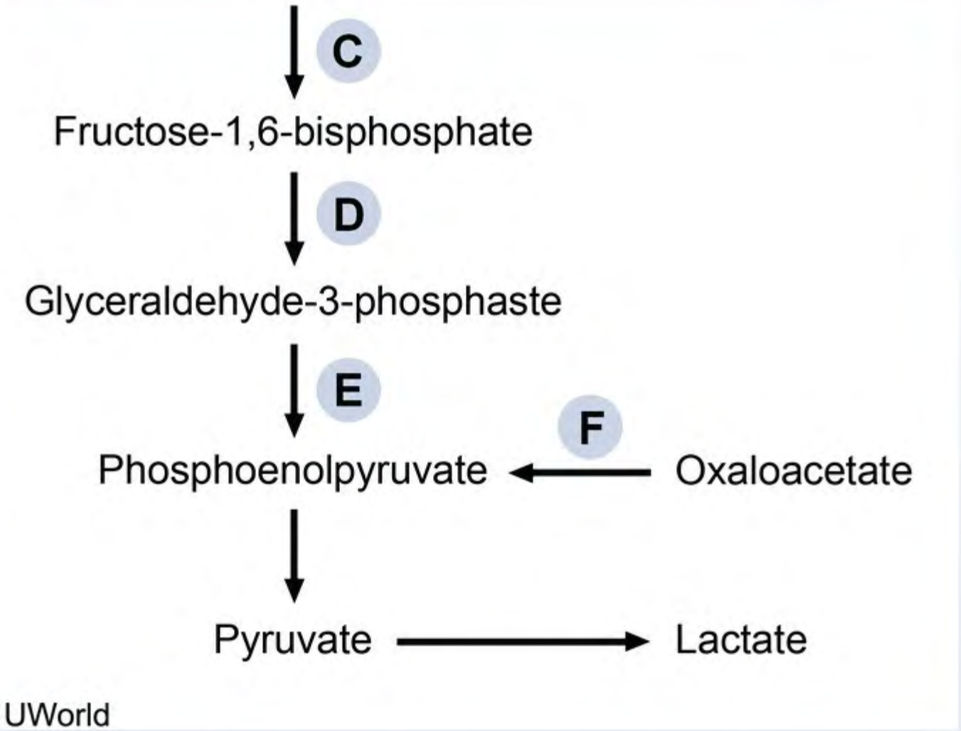


©UWorld

Zoom In Zoom Out Reset New | Existing My Notebook

Glyceraldehyde-3-phosphaste

https://t.me/USMLEWorldStep1

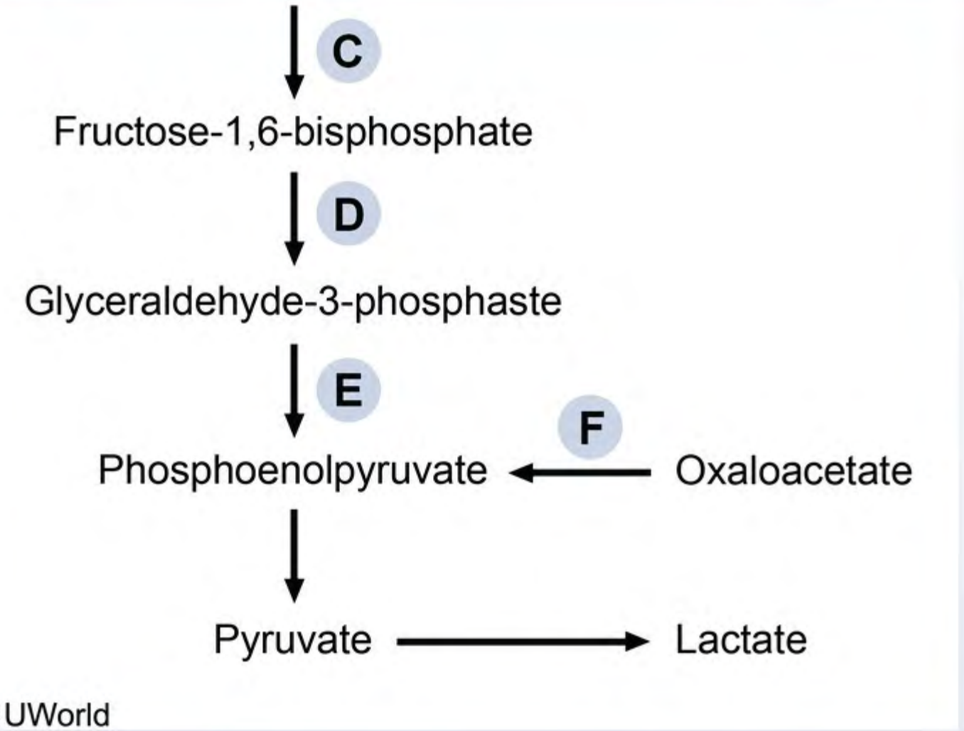


©UWorld

- A. A
- B. B
- C. C
- D. D
- E. E
- F. F

Submit

https://t.me/USMLEWorldStep1



- A. A (20%)
- ✗ B. B (9%)
- ✓ C. C (43%)
- D. D (5%)
- E. E (3%)
- F. F (18%)

Incorrect
Correct answer
C

43%
Answered correctly

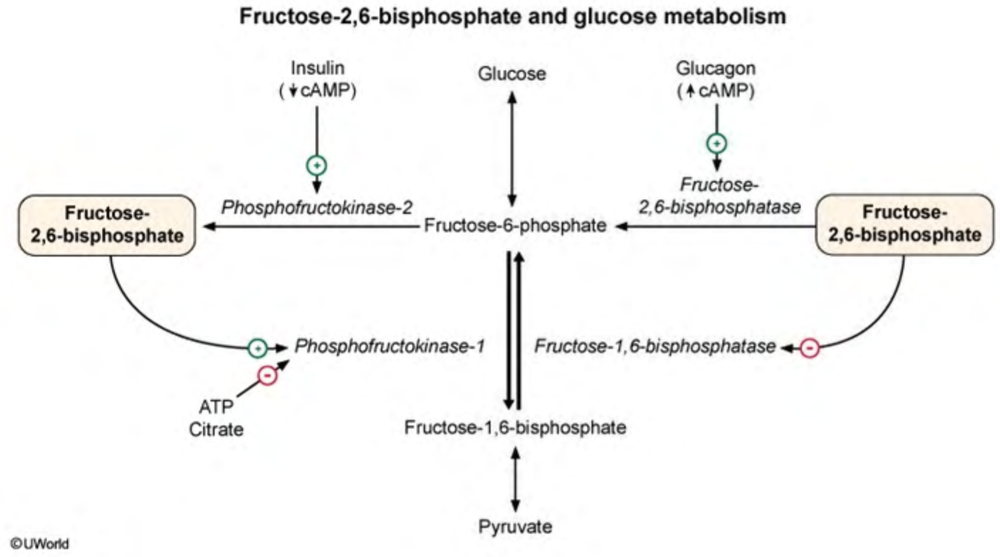
14 secs
Time Spent

2023
Version

https://t.me/USMLEWorldStep1

E. E (3%)

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

This p
Hypog
inadve
(eg, gl

Insulin

increase in glycolysis by **activating** phosphofructokinase-2 (**PFK2**), the enzyme that produces fructose 2,6-

https://t.me/USMLEWorldStep1



©UWorld

This patient has developed **hypoglycemia** secondary to **increased levels of an endogenous hormone**. Hypoglycemia can develop due to **insulin excess** (either endogenous [eg, insulinoma] or exogenous [eg, inadvertent overdose, surreptitious insulin/secretagogue use]) as well as deficiency of counterregulatory hormones (eg, glucagon, epinephrine, cortisol).

Insulin lowers plasma glucose by increasing glucose uptake in fat, muscle, and liver. In addition, insulin causes an **increase in glycolysis** by **activating** phosphofructokinase-2 (**PFK2**), the enzyme that produces fructose 2,6-bisphosphate. The intracellular concentration of fructose 2,6-bisphosphate is the major regulator of phosphofructokinase-1 (**PFK1**), which **converts fructose 6-phosphate** to **fructose 1,6-bisphosphate** in the rate-limiting step of glycolysis. Fructose 2,6-bisphosphate stimulates PFK1 while inhibiting the reverse enzyme, fructose 1,6-bisphosphatase. As a result, the rise in fructose 2,6-bisphosphate levels caused by insulin leads to an increase in glycolysis and inhibition of gluconeogenesis, with a corresponding **decrease** in circulating **glucose levels**.

(Choice A) Insulin promotes the storage of glucose by *inhibiting* glycogen phosphorylase (breaks down glycogen into glucose-6-phosphate) and stimulating glycogen synthase (incorporates UDP-glucose into glycogen).

(Choices B, D, and E) Glucose 6-phosphate is converted to fructose 6-phosphate by phosphoglucose isomerase. Fructose 1,6-bisphosphate is converted to glyceraldehyde 3-phosphate and dihydroxyacetone phosphate by fructose bisphosphate aldolase. Glyceraldehyde 3-phosphate is converted to phosphoenolpyruvate through the action of multiple enzymes. These steps are readily reversible and not regulated by insulin.

(Choice F) Oxaloacetate is converted to phosphoenolpyruvate by phosphoenolpyruvate carboxykinase during gluconeogenesis; this reaction is *downregulated* by high insulin levels.

Educational objective:
Phosphofructokinase-1 (PFK1) catalyzes the rate-limiting step in glycolysis, and the most potent stimulator of PFK1 is fructose 2,6-bisphosphate. Insulin increases production of fructose 2,6-bisphosphate by phosphofructokinase-2 (PFK2), thereby stimulating glycolysis.

References

https://t.me/USMLEWorldStep1

Pyruvate

This p
Hypog
inadve
(eg, gl

Insulin
increa
bispho
phosp
limiting
fructos
increa
levels

(Choi
into gl

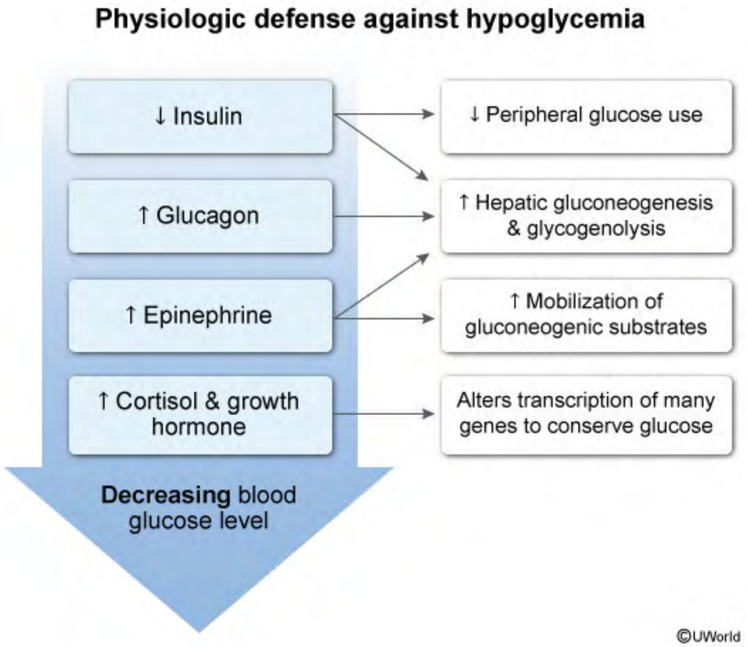
(Choi
isomer
phosp
throug

(Choi
glucon

Educa
Phosp
PFK1
phosphofructokinase-2 (PFK2), thereby stimulating glycolysis.

References

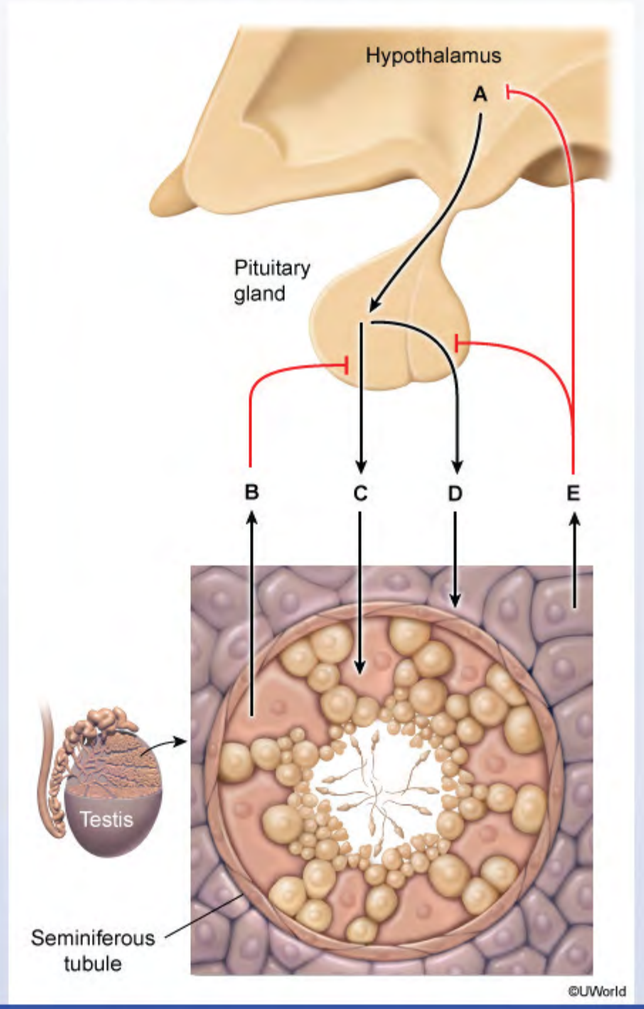
Exhibit Display



Zoom In Zoom Out Reset New | Existing My Notebook

https://t.me/USMLEWorldStep1

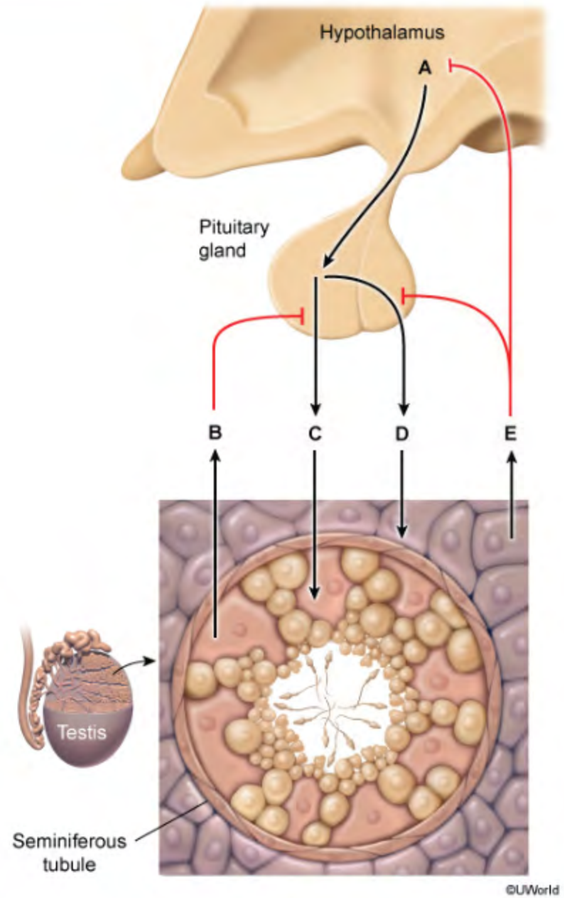
A 14-year-old boy is brought to the physician by his mother. She is concerned because although tall, her son looks much younger than his peers and shows no signs of "masculinity." On physical examination, the boy has poorly developed secondary sexual characteristics. He is unable to distinguish smells but has good visual acuity. Which of the following pathways is most likely defective in this patient?



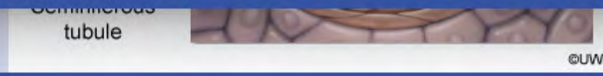
https://t.me/USMLEWorldStep1

A 14-year-old boy is brought to the physician by his mother. She is concerned because although tall, her son looks much
develo
of the

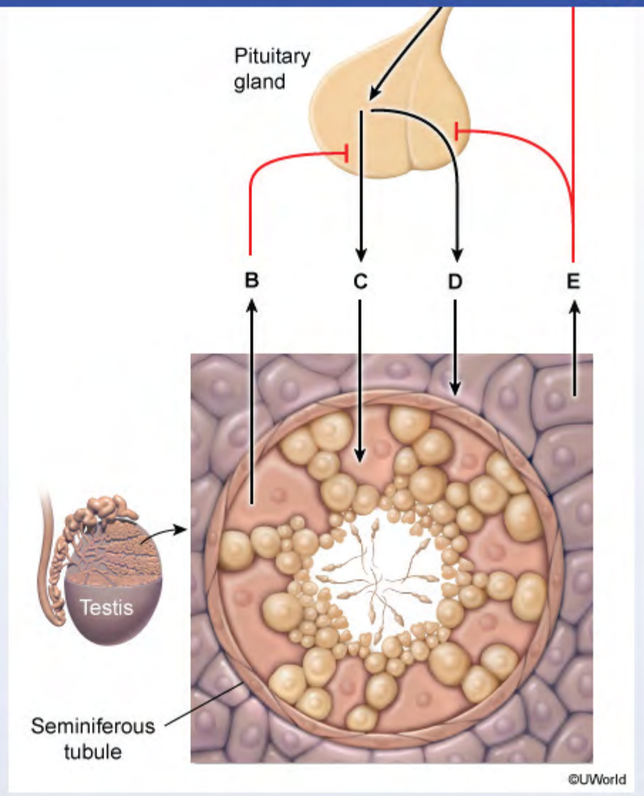
Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook



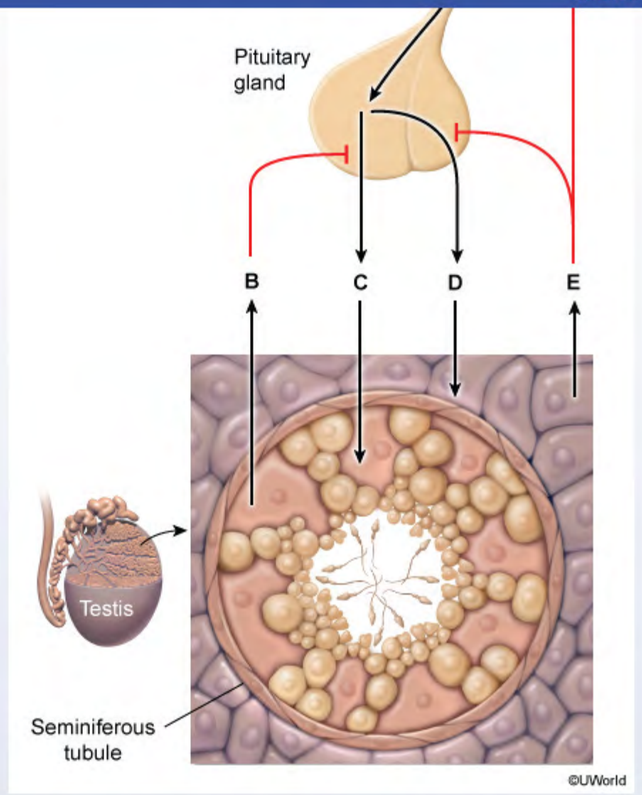
https://t.me/USMLEWorldStep1



- A. A
- B. B
- C. C
- D. D
- E. E

Submit

https://t.me/USMLEWorldStep1



- ✓ ○ A. A (57%)
- ○ B. B (4%)
- ○ C. C (8%)
- ○ D. D (20%)
- ✗ ◉ E. E (8%)

Incorrect
Correct answer
A

57%
Answered correctly

18 secs
Time Spent

2023
Version

https://t.me/USMLEWorldStep1

Explanation

This patient has delayed puberty plus anosmia, consistent with a diagnosis of Kallmann syndrome. Kallmann syndrome results from a failure of GnRH-secreting neurons to migrate from their origin in the olfactory placode (situated outside the central nervous system) to their normal anatomic location in the hypothalamus. Most often, the cause is a mutation in the KAL-1 gene or the fibroblast growth factor receptor-1 gene, which code for proteins required in this migration.

Patients with Kallmann syndrome classically have central hypogonadism and anosmia, although there may be other midline defects as well (eg, cleft lip or cleft palate). Most often, these patients present with delayed puberty. On physical examination, the testes are often just 1-2 mL in volume. There is usually some pubic hair because adrenarche occurs normally.

In the United States, delayed puberty is defined as the absence or incomplete development of secondary sexual characteristics by age 14 in boys and by age 12 in girls. Testicular enlargement is the first sign of puberty in boys, and breast enlargement is the first sign in girls. The initiation of puberty and the maintenance of secondary sexual characteristics and fertility require the coordinated efforts of the hypothalamus, pituitary, and gonads. Delayed puberty can result from a derangement anywhere in this axis.

(Choices B, C, D, and E) These pathways represent normal feedback loops between the testes and the hypothalamus and pituitary. Pituitary follicle-stimulating hormone (FSH) stimulates proliferation of the seminiferous tubules and spermatogenesis. The seminiferous tubules produce inhibin, which feeds back to inhibit pituitary FSH secretion. Luteinizing hormone from the pituitary stimulates the interstitial Leydig cells to produce testosterone, which also participates in feedback inhibition.

Educational objective:
In Kallmann syndrome, there is an absence of GnRH secretory neurons in the hypothalamus due to defective migration from the olfactory placode. These patients have central hypogonadism and anosmia, and often present with delayed puberty.

Pathology	Endocrine, Diabetes & Metabolism	Kallmann syndrome
Subject	System	Topic

https://t.me/USMLEWorldStep1

Explanation

This p
syndro
(situat
the ca
require

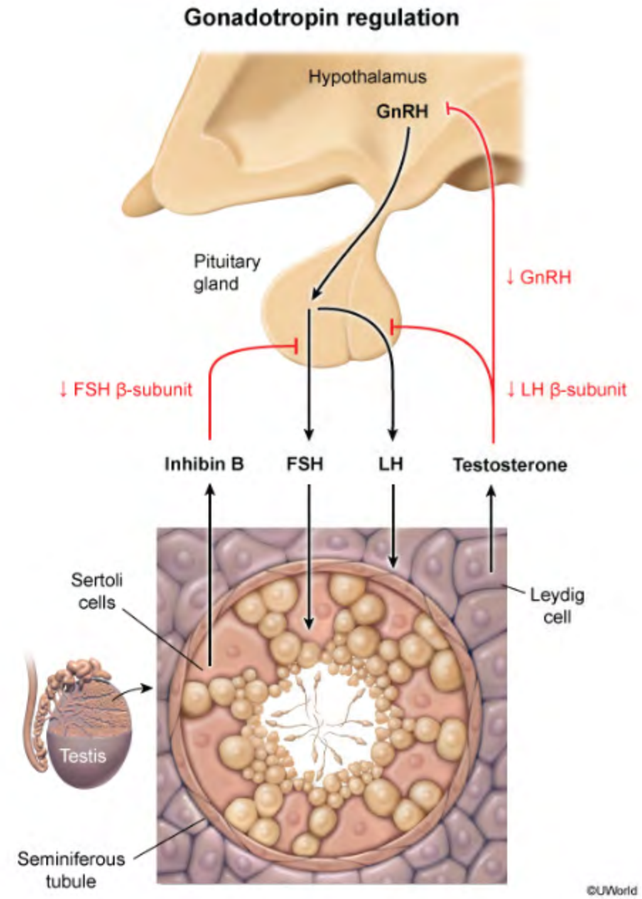
Patien
other r
On ph
adrena

In the
charac
and br
charac
pubert

(Choi
hypoth
tubule
secret
which

Educa
In Kall
migrat
with de

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Pathology (Subject) | Endocrine, Diabetes & Metabolism (System) | Kallmann syndrome (Topic)

https://t.me/USMLEWorldStep1

A 32-year-old woman comes to the office due to neck swelling. The patient says her neck has gradually gotten larger, and she does not like how it appears in the mirror. She otherwise feels well and has no hoarseness, trouble swallowing, or shortness of breath. There is no history of head and neck irradiation. The patient has no prior medical conditions and takes no medications. She has a sister with vitiligo. Blood pressure is 110/60 mm Hg and pulse is 75/min. On physical examination, the thyroid is diffusely enlarged with no palpable nodules. There is no tracheal deviation. Serum TSH and free thyroxine levels are normal. Antibodies against thyroid peroxidase are present in high titers. The antigenic target of these antibodies is involved in which of the following processes?

- A. Iodide uptake
- B. Iodotyrosine deiodination
- C. Thyroglobulin iodination
- D. Thyroglobulin synthesis
- E. Thyroxine to triiodothyronine conversion

Submit

https://t.me/USMLEWorldStep1

A 32-year-old woman comes to the office due to neck swelling. The patient says her neck has gradually gotten larger, and she does not like how it appears in the mirror. She otherwise feels well and has no hoarseness, trouble swallowing, or shortness of breath. There is no history of head and neck irradiation. The patient has no prior medical conditions and takes no medications. She has a sister with vitiligo. Blood pressure is 110/60 mm Hg and pulse is 75/min. On physical examination, the thyroid is diffusely enlarged with no palpable nodules. There is no tracheal deviation. Serum TSH and free thyroxine levels are normal. Antibodies against thyroid peroxidase are present in high titers. The antigenic target of these antibodies is involved in which of the following processes?

- A. Iodide uptake (4%)
- ✗ B. Iodotyrosine deiodination (5%)
- ✓ C. Thyroglobulin iodination (69%)
- D. Thyroglobulin synthesis (8%)
- E. Thyroxine to triiodothyronine conversion (11%)

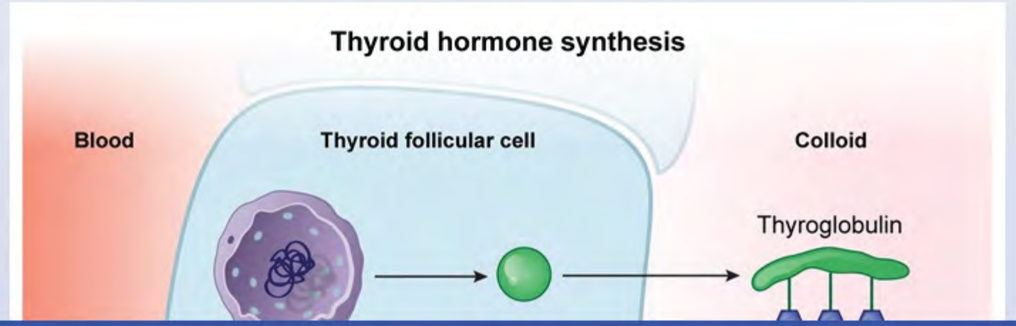
Incorrect
Correct answer
C

69%
Answered correctly

03 secs
Time Spent

2023
Version

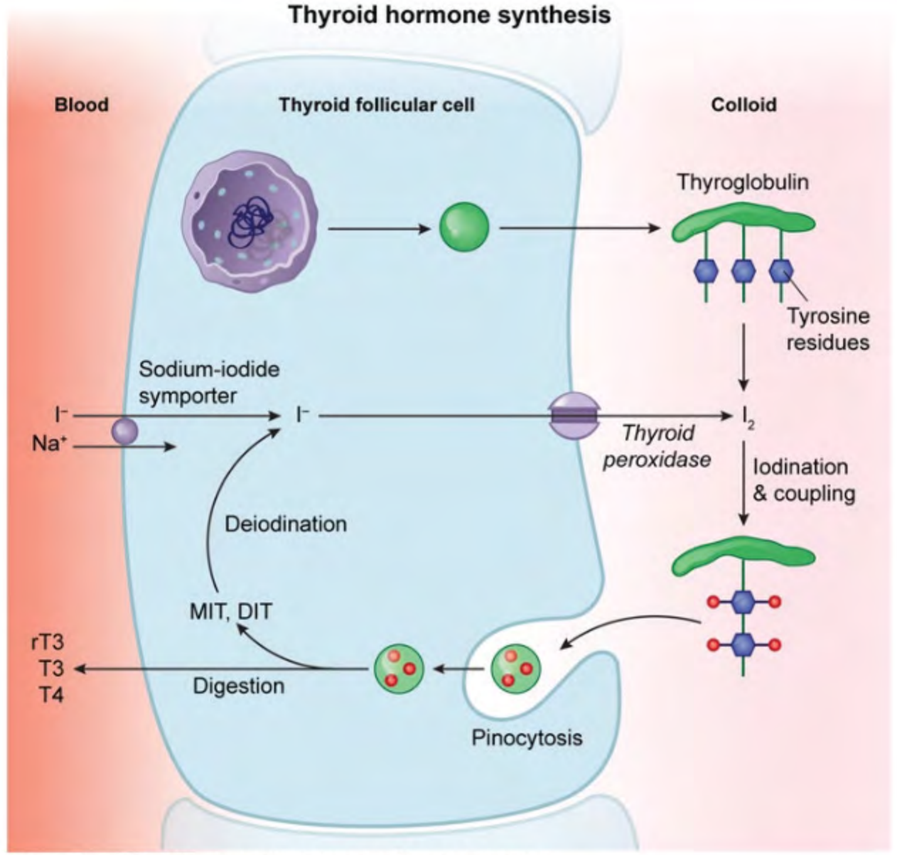
Explanation



https://t.me/USMLEWorldStep1

A 32-year-old woman comes to the office due to neck swelling. The patient says her neck has gradually gotten larger, swallo medica pulse i trache preser

Exhibit Display



DIT = diiodotyrosine; **rT3** = reverse triiodothyronine; **T3** = triiodothyronine; **T4** = thyroxine; **MIT** = monoiodotyrosine.

©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

DIT = diiodotyrosine; **rT3** = reverse triiodothyronine; **T3** = triiodothyronine; **T4** = thyroxine; **MIT** = monoiodotyrosine.

©UWorld

Thyroid follicular cells take up iodide (I^-), which is then transported into the thyroid follicular lumen, where it is oxidized to iodine (I_2). Following oxidation, in a process referred to as organification, iodine reacts with tyrosine residues in thyroglobulin to form monoiodotyrosine (MIT) and diiodotyrosine (DIT) (iodination). While still attached to thyroglobulin, DIT and MIT participate in 2 coupling reactions: The coupling of 2 DITs results in formation of **thyroxine** (T4); the combination of 1 DIT and 1 MIT leads to the formation of **triiodothyronine** (T3). Subsequently, thyroglobulin, which is now attached to multiple iodinated tyrosine compounds (ie, MIT, DIT, T3, T4), is engulfed by the thyroid follicular cells and digested within lysosomes, releasing T3 and T4 into the circulation. Free DIT and MIT are also produced, but only small amounts are secreted because iodotyrosine deiodinase removes the iodine groups from MIT and DIT for recycling **(Choice B)**.

Thyroid peroxidase (TPO) is a multifunctional enzyme that catalyzes the oxidation of iodide, the iodination of thyroglobulin, and the coupling reaction between 2 iodized tyrosine residues. Antibodies against TPO can be seen in a variety of autoimmune thyroid disorders, most commonly chronic lymphocytic (Hashimoto) thyroiditis (90% of patients). Hashimoto thyroiditis is a common cause of diffuse goiter, as in this patient. Although most patients develop residual hypothyroidism (low T4, elevated TSH), early in the disease they may be euthyroid (normal T4, normal TSH) or briefly hyperthyroid (elevated T4, suppressed TSH).

(Choice A) Uptake of iodide from the blood against its concentration gradient is an energy-dependent process carried out by the sodium-iodide symporter and stimulated by TSH. TPO is not involved in iodide uptake.

(Choice D) Thyroglobulin is a high-molecular-weight, glycosylated protein that is the major component of colloid in the thyroid follicle. TPO is involved in iodination, but not synthesis of thyroglobulin.

(Choice E) As noted above, the thyroid produces both T3 and T4, although most is in the form of T4. T3, the more active form of thyroid hormone, is produced primarily in peripheral tissues by deiodination of T4. This reaction is catalyzed by iodothyronine deiodinase, not by TPO.

Educational objective:
Thyroid peroxidase (TPO) catalyzes the oxidation of iodide to iodine, the iodination of thyroglobulin tyrosine residues, and the iodotyrosine coupling reaction that forms T3 and T4. Antibodies against TPO are present in

https://t.me/USMLEWorldStep1

oxidized to iodine (I_2). Following oxidation, in a process referred to as organification, iodine reacts with tyrosine residues in thyroglobulin to form monoiodotyrosine (MIT) and diiodotyrosine (DIT) (iodination). While still attached to thyroglobulin, DIT and MIT participate in 2 coupling reactions: The coupling of 2 DITs results in formation of **thyroxine** (T4); the combination of 1 DIT and 1 MIT leads to the formation of **triiodothyronine** (T3). Subsequently, thyroglobulin, which is now attached to multiple iodinated tyrosine compounds (ie, MIT, DIT, T3, T4), is engulfed by the thyroid follicular cells and digested within lysosomes, releasing T3 and T4 into the circulation. Free DIT and MIT are also produced, but only small amounts are secreted because iodotyrosine deiodinase removes the iodine groups from MIT and DIT for recycling **(Choice B)**.

Thyroid peroxidase (TPO) is a multifunctional enzyme that catalyzes the oxidation of iodide, the iodination of thyroglobulin, and the coupling reaction between 2 iodized tyrosine residues. Antibodies against TPO can be seen in a variety of autoimmune thyroid disorders, most commonly chronic lymphocytic (Hashimoto) thyroiditis (90% of patients). Hashimoto thyroiditis is a common cause of diffuse goiter, as in this patient. Although most patients develop residual hypothyroidism (low T4, elevated TSH), early in the disease they may be euthyroid (normal T4, normal TSH) or briefly hyperthyroid (elevated T4, suppressed TSH).

(Choice A) Uptake of iodide from the blood against its concentration gradient is an energy-dependent process carried out by the sodium-iodide symporter and stimulated by TSH. TPO is not involved in iodide uptake.

(Choice D) Thyroglobulin is a high-molecular-weight, glycosylated protein that is the major component of colloid in the thyroid follicle. TPO is involved in iodination, but not synthesis of thyroglobulin.

(Choice E) As noted above, the thyroid produces both T3 and T4, although most is in the form of T4. T3, the more active form of thyroid hormone, is produced primarily in peripheral tissues by deiodination of T4. This reaction is catalyzed by iodothyronine deiodinase, not by TPO.

Educational objective:
Thyroid peroxidase (TPO) catalyzes the oxidation of iodide to iodine, the iodination of thyroglobulin tyrosine residues, and the iodotyrosine coupling reaction that forms T3 and T4. Antibodies against TPO are present in >90% of patients with chronic lymphocytic (Hashimoto) thyroiditis.

Physiology	Endocrine, Diabetes & Metabolism	Hypothyroidism
Subject	System	Topic

https://t.me/USMLEWorldStep1

A 16-year-old boy is brought to the emergency department because of confusion, fatigue, and abdominal pain. He has also experienced excessive thirst and polyuria during the last 3 weeks. His past medical history is insignificant. Family history is unremarkable. Urine dipstick is positive for glucose and ketones. Which of the following factors most likely contributed to the development of this patient's condition?

- A. Abdominal fat distribution
- B. Excessive body weight
- C. Genetic defects in insulin secretion
- D. Islet amyloid deposition
- E. Islet leukocytic infiltration

Submit

https://t.me/USMLEWorldStep1

A 16-year-old boy is brought to the emergency department because of confusion, fatigue, and abdominal pain. He has also experienced excessive thirst and polyuria during the last 3 weeks. His past medical history is insignificant. Family history is unremarkable. Urine dipstick is positive for glucose and ketones. Which of the following factors most likely contributed to the development of this patient's condition?

- A. Abdominal fat distribution (1%)
- ✗ B. Excessive body weight (2%)
- C. Genetic defects in insulin secretion (19%)
- D. Islet amyloid deposition (5%)
- ✓ E. Islet leukocytic infiltration (71%)

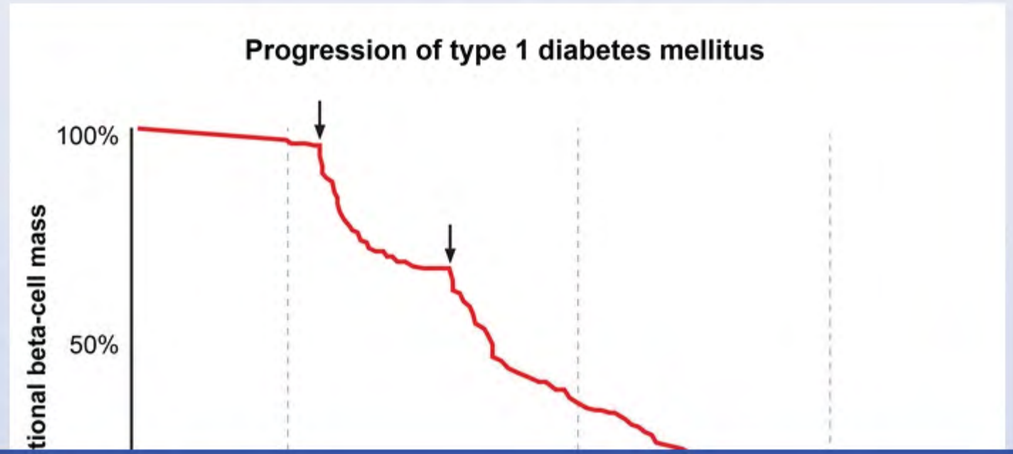
Incorrect
Correct answer
E

71%
Answered correctly

03 secs
Time Spent

2023
Version

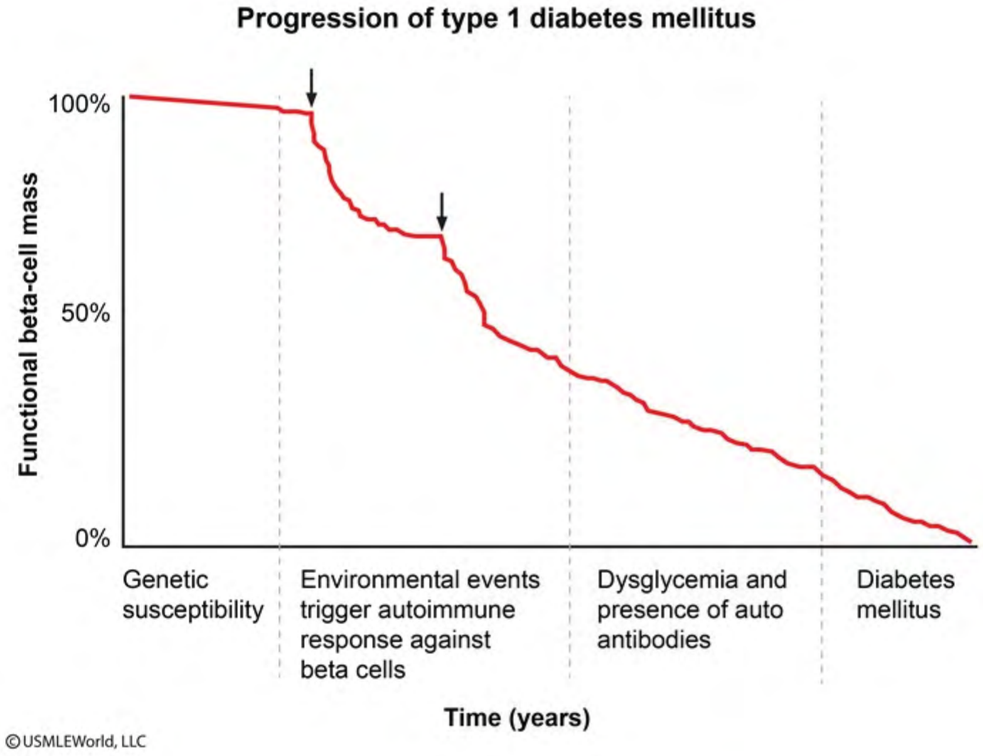
Explanation



https://t.me/USMLEWorldStep1

A 16-year-old boy is brought to the emergency department because of confusion, fatigue, and abdominal pain. He has al
insigni
followi

Exhibit Display



Zoom In Zoom Out Reset New | Existing My Notebook

https://t.me/USMLEWorldStep1

This patient is presenting with diabetic ketoacidosis, a condition that most commonly affects patients with **type 1 diabetes mellitus** due to their absolute insulin deficiency. Type 1 diabetes mellitus occurs in genetically susceptible individuals who are exposed to triggering environmental factors (eg, viral infections, environmental toxins, dietary components). This results in an **autoimmune response** against **pancreatic beta cells** that leads to progressive loss of beta cell mass. Overt manifestations of diabetes mellitus tend to develop once >90% of beta cells are destroyed. Although antibodies against islet antigens are detected in a large number of patients, they are thought to play a permissive role in disease pathogenesis; the destruction of beta cells occurs primarily through **cell-mediated immunity**. Infiltration of islets by inflammatory cells is called **insulitis** and is more prominent during the early stages of disease.

(Choices A and B) Abdominal fat deposition and excessive body weight are important contributors to insulin resistance and development of type 2 diabetes mellitus. Intra-abdominal visceral fat is more strongly related to insulin resistance than is subcutaneous fat.

(Choice C) Maturity-onset diabetes of the young is an autosomal dominant disease caused by mutations that impair glucose sensing and insulin secretion by pancreatic beta cells. It presents as non-insulin-dependent diabetes at a young age (<25) and accounts for <5% of all cases of diabetes mellitus.

(Choice D) Islet amyloid polypeptide is secreted along with insulin from pancreatic beta cells. Amyloid deposition occurs in the islets of patients with type 2 diabetes mellitus, although its role as a causative agent of beta cell dysfunction remains unknown. Patients with type 1 diabetes mellitus have low circulating levels of islet amyloid polypeptide due to extensive beta cell destruction.

Educational objective:
Autoimmune insulitis with progressive beta cell loss is the most common cause of type 1 diabetes mellitus. Insulin resistance accompanied by relative insulin deficiency is the main cause of type 2 diabetes mellitus.

References

- Advances in the cellular immunological pathogenesis of type 1 diabetes.

Pathology	Endocrine, Diabetes & Metabolism	Diabetes mellitus
Subject	System	Topic

https://t.me/USMLEWorldStep1

A 43-year-old woman comes to the office to discuss amenorrhea. She began having irregular menses 2 years ago, and her last menstrual period was 9 months ago. Family history is unremarkable. Laboratory studies show an increased serum prolactin level, a normal TSH level, and an undetectable β-hCG concentration. Serum calcium is normal. MRI reveals a 6-mm pituitary adenoma. The patient refuses medical and surgical therapy as she is happy about not having menstrual periods. If left untreated, this patient is at greatest risk of developing which of the following?

- A. Cortical stroke
- B. Gastric ulcer
- C. Loss of bone mass
- D. Myocardial infarction
- E. Secondary diabetes mellitus

Submit

https://t.me/USMLEWorldStep1

A 43-year-old woman comes to the office to discuss amenorrhea. She began having irregular menses 2 years ago, and her last menstrual period was 9 months ago. Family history is unremarkable. Laboratory studies show an increased serum prolactin level, a normal TSH level, and an undetectable β-hCG concentration. Serum calcium is normal. MRI reveals a 6-mm pituitary adenoma. The patient refuses medical and surgical therapy as she is happy about not having menstrual periods. If left untreated, this patient is at greatest risk of developing which of the following?

- A. Cortical stroke (12%)
- ✗ B. Gastric ulcer (2%)
- ✓ C. Loss of bone mass (75%)
- D. Myocardial infarction (2%)
- E. Secondary diabetes mellitus (7%)

Incorrect
Correct answer
C

75%
Answered correctly

04 secs
Time Spent

2023
Version

Explanation

Prolactinoma	
Clinical features	• **Premenopausal women**: oligomenorrhea/amenorrhea, infertility, galactorrhea, hot flashes, decreased bone density • **Postmenopausal women**: mass-effect symptoms (headache, visual field defects) • **Men**: infertility, decreased libido, impotence, gynecomastia
Laboratory/ imaging	• Serum prolactin (often >200 ng/mL) • Tests to rule out renal insufficiency (creatinine) & hypothyroidism (TSH, thyroxine)

https://t.me/USMLEWorldStep1

Prolactinoma	
Clinical features	• **Premenopausal women**: oligomenorrhea/amenorrhea, infertility, galactorrhea, hot flashes, decreased bone density • **Postmenopausal women**: mass-effect symptoms (headache, visual field defects) • **Men**: infertility, decreased libido, impotence, gynecomastia
Laboratory/ imaging	• Serum prolactin (often >200 ng/mL) • Tests to rule out renal insufficiency (creatinine) & hypothyroidism (TSH, thyroxine) • MRI of the head/pituitary
Treatment	• Dopamine agonist (cabergoline) • Transsphenoidal surgery

This patient's small **pituitary adenoma** with an **elevated prolactin** level and **secondary amenorrhea** is consistent with a prolactin-secreting adenoma **(prolactinoma)**. High levels of prolactin suppress GnRH secretion from the hypothalamus, leading to reduced secretion of LH (and to a lesser extent FSH) and subsequent **hypogonadism**. Nonsecretory ("nonfunctioning") adenomas can also cause mild hyperprolactinemia due to pressure on the stalk, but these tumors primarily cause mass-effect symptoms (eg, hypopituitarism, headache, bitemporal hemianopsia) due to pressure on surrounding structures.

Estrogen maintains bone mass in premenopausal women. Low estrogen levels lead to increased production of inflammatory cytokines (especially IL-1 and tumor necrosis factor–alpha), increasing expression of the receptor activator of nuclear factor kappa B ligand (RANKL) and resulting in increased osteoclast activity. Loss of estrogen, whether from menopause, ovulatory dysfunction, or surgical removal of the ovaries, increases the risk of bone loss and **osteoporosis**.

(Choice A) Adenomas are associated with pituitary apoplexy (hemorrhage into the pituitary). However, this occurs more commonly with large adenomas and is not typically associated with strokes located in the cortex.

(Choice B) Multiple endocrine neoplasia (MEN) type 1 is characterized by pituitary adenomas, hyperparathyroidism, and endocrine tumors of the pancreas. Gastrin-secreting pancreatic tumors are common

https://t.me/USMLEWorldStep1

Treatment	• Dopamine agonist (cabergoline) • Transsphenoidal surgery

This patient's small **pituitary adenoma** with an **elevated prolactin** level and **secondary amenorrhea** is consistent with a prolactin-secreting adenoma **(prolactinoma)**. High levels of prolactin suppress GnRH secretion from the hypothalamus, leading to reduced secretion of LH (and to a lesser extent FSH) and subsequent **hypogonadism**. Nonsecretory ("nonfunctioning") adenomas can also cause mild hyperprolactinemia due to pressure on the stalk, but these tumors primarily cause mass-effect symptoms (eg, hypopituitarism, headache, bitemporal hemianopsia) due to pressure on surrounding structures.

Estrogen maintains bone mass in premenopausal women. Low estrogen levels lead to increased production of inflammatory cytokines (especially IL-1 and tumor necrosis factor–alpha), increasing expression of the receptor activator of nuclear factor kappa B ligand (RANKL) and resulting in increased osteoclast activity. Loss of estrogen, whether from menopause, ovulatory dysfunction, or surgical removal of the ovaries, increases the risk of bone loss and **osteoporosis**.

(Choice A) Adenomas are associated with pituitary apoplexy (hemorrhage into the pituitary). However, this occurs more commonly with large adenomas and is not typically associated with strokes located in the cortex.

(Choice B) Multiple endocrine neoplasia (MEN) type 1 is characterized by pituitary adenomas, hyperparathyroidism, and endocrine tumors of the pancreas. Gastrin-secreting pancreatic tumors are common and may lead to recurrent peptic ulcers (Zollinger-Ellison syndrome). However, almost all patients with MEN type 1 have hyperparathyroidism with hypercalcemia.

(Choice D) Early menopause (age <40) is associated with an increased risk of cardiovascular events, but the effect of the prolactinoma-induced low estrogenic state on cardiovascular risk in older women is unclear.

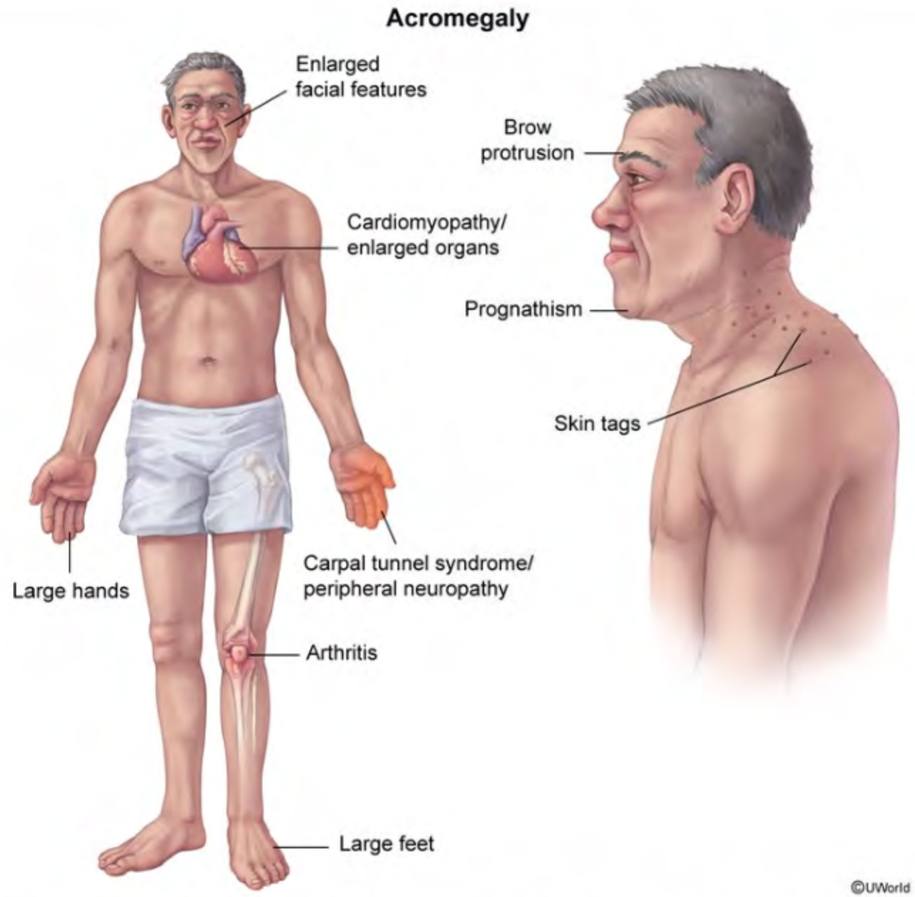
(Choice E) Excess growth hormone secretion from a somatotroph pituitary adenoma can lead to diabetes mellitus due to increased insulin resistance in peripheral tissues. However, adults typically present with acromegaly.

Educational objective:
Hyperprolactinemia suppresses secretion of GnRH, which leads to reduced estrogen in women. Low estrogen levels are a risk factor for accelerated bone loss.

https://t.me/USMLEWorldStep1

Treatment	• Dopamine agonist (cabergoline) • Transsphenoidal surgery

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

This p
consis
from th
hypog
pressu
bitemp

Estrog
inflam
activat
whethe
and **os**

(Choi
more

(Choi
hyperp
and m
have h

(Choi
effect

(Choi
due to

Educa
Hyperp
levels are a risk factor for accelerated bone loss.

https://t.me/USMLEWorldStep1

A 56-year-old man comes to the office for follow-up of type 2 diabetes mellitus. The patient has had inadequate glycemic control with metformin monotherapy; an additional medication that inhibits dipeptidyl peptidase-4 was prescribed 3 months ago. The patient also has hypertension for which he takes ramipril. He does not use tobacco, alcohol, or recreational drugs. The patient says he is generally compliant with dietary guidance but occasionally eats fast food. Blood pressure is 126/74 mm Hg and pulse is 76/min. BMI is 31.4 kg/m^2. Physical examination shows no abnormalities. Laboratory results show a hemoglobin A1c of 6.8%. The newly prescribed medication most likely improved this patient's glycemic control through which of the following mechanisms?

- A. Decreased dietary carbohydrate digestion
- B. Decreased renal glucose reabsorption
- C. Increased glucagon secretion
- D. Increased glucose-dependent insulin release
- E. Increased peripheral tissue glucose uptake

Submit

https://t.me/USMLEWorldStep1

A 56-year-old man comes to the office for follow-up of type 2 diabetes mellitus. The patient has had inadequate glycemic control with metformin monotherapy; an additional medication that inhibits dipeptidyl peptidase-4 was prescribed 3 months ago. The patient also has hypertension for which he takes ramipril. He does not use tobacco, alcohol, or recreational drugs. The patient says he is generally compliant with dietary guidance but occasionally eats fast food. Blood pressure is 126/74 mm Hg and pulse is 76/min. BMI is 31.4 kg/m^2. Physical examination shows no abnormalities. Laboratory results show a hemoglobin A1c of 6.8%. The newly prescribed medication most likely improved this patient's glycemic control through which of the following mechanisms?

- A. Decreased dietary carbohydrate digestion (10%)
- ✗ B. Decreased renal glucose reabsorption (5%)
- C. Increased glucagon secretion (6%)
- ✓ D. Increased glucose-dependent insulin release (63%)
- E. Increased peripheral tissue glucose uptake (13%)

Incorrect
Correct answer
D

63%
Answered correctly

04 secs
Time Spent

2023
Version

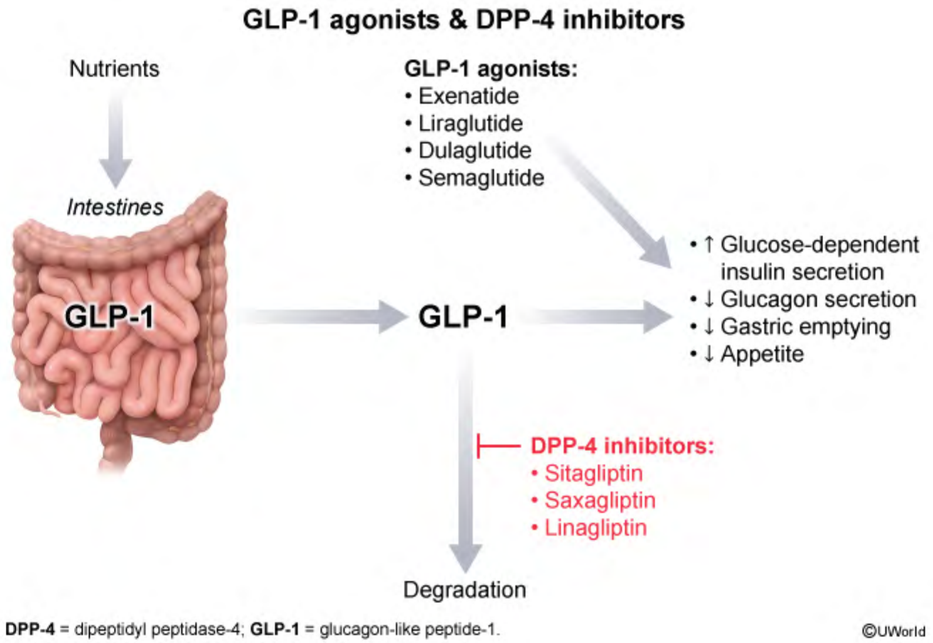
Explanation



https://t.me/USMLEWorldStep1

B. Decreased renal glucose reabsorption (5%)

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Glucagon-like peptide-1 (GLP-1) is secreted by intestinal L cells in response to food intake and regulates glucose

https://t.me/USMLEWorldStep1

Glucagon-like peptide-1 (GLP-1) is secreted by intestinal L cells in response to food intake and regulates glucose levels by slowing gastric emptying, suppressing glucagon secretion, and **increasing glucose-dependent insulin release**. It acts through cell surface receptors and is degraded by dipeptidyl peptidase-4 (DPP-4), which is found on the cell surface and in the circulation.

DPP-4 inhibitors (eg, sitagliptin, saxagliptin) **inhibit degradation of GLP-1**, prolonging its effects and leading to improved glycemic control (eg, hemoglobin A1c reduction). GLP-1's effect on insulin secretion is glucose dependent: as glucose levels fall (ie, fasting state), so does insulin secretion; therefore, the risk of hypoglycemia is low.

GLP-1 agonists (eg, exenatide) are also available; they are intrinsically resistant to DPP-4 and have a similar (but more potent) effect in lowering blood glucose with a low risk of hypoglycemia.

(Choice A) Alpha-glucosidase inhibitors (eg, acarbose) impair the hydrolysis (ie, digestion) of polymeric carbohydrates, leading to decreased postprandial glucose absorption. Although DPP-4 inhibitors can delay gastric emptying, they do not decrease the digestion of carbohydrates.

(Choice B) Sodium-glucose cotransporter 2 inhibitors (eg, canagliflozin, dapagliflozin) act in the kidney to decrease reabsorption of filtered glucose.

(Choice C) GLP-1 acts directly on pancreatic islet cells to suppress (not increase) glucagon secretion, an effect that is enhanced by DPP-4 inhibitors.

(Choice E) Metformin inhibits mitochondrial enzymes required for gluconeogenesis, leading to decreased hepatic glucose production and lower circulating glucose levels. It also increases peripheral glucose uptake and improves insulin sensitivity by activating AMP-activated protein kinase.

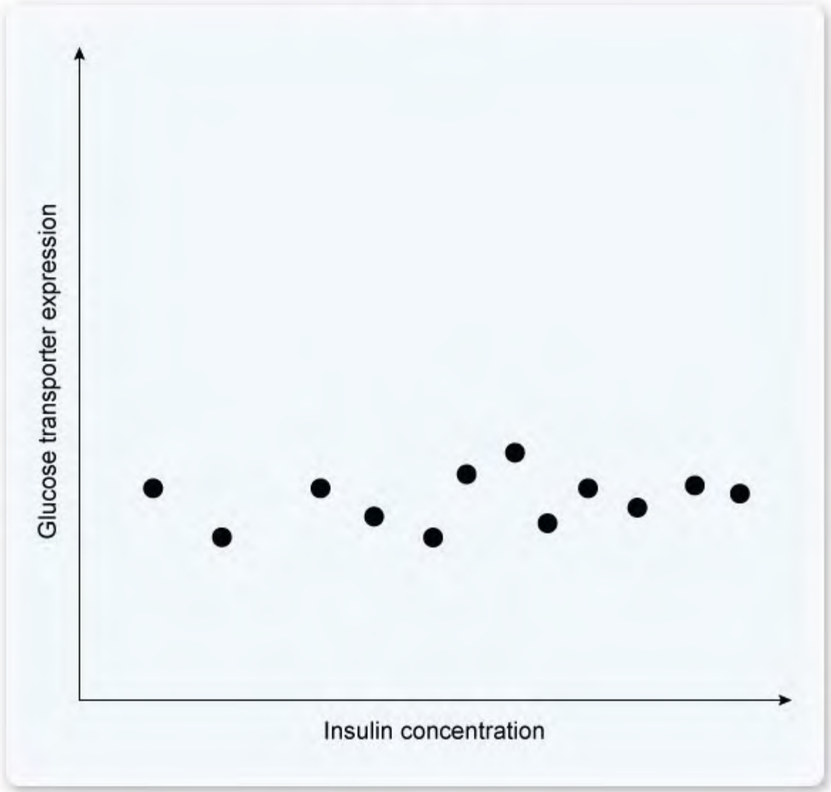
Educational objective:
Glucagon-like peptide-1 (GLP-1), degraded by dipeptidyl peptidase-4 (DPP-4), helps regulate blood glucose by slowing gastric emptying, suppressing glucagon secretion, and increasing glucose-dependent insulin release. DPP-4 inhibitors (eg, sitagliptin) increase the effects of GLP-1 and improve glycemic control. Because the effect on insulin is glucose dependent, there is minimal risk of hypoglycemia.

References

https://t.me/USMLEWorldStep1

Researchers are investigating the relationship between glucose transport proteins and insulin concentration in different types of tissues. Experiments in which cells are taken from various tissue samples and exposed to increasing concentrations of insulin are performed. The number of surface glucose transporters are then measured. The results from 2 cell samples are plotted on the graphs below.

Cell sample A



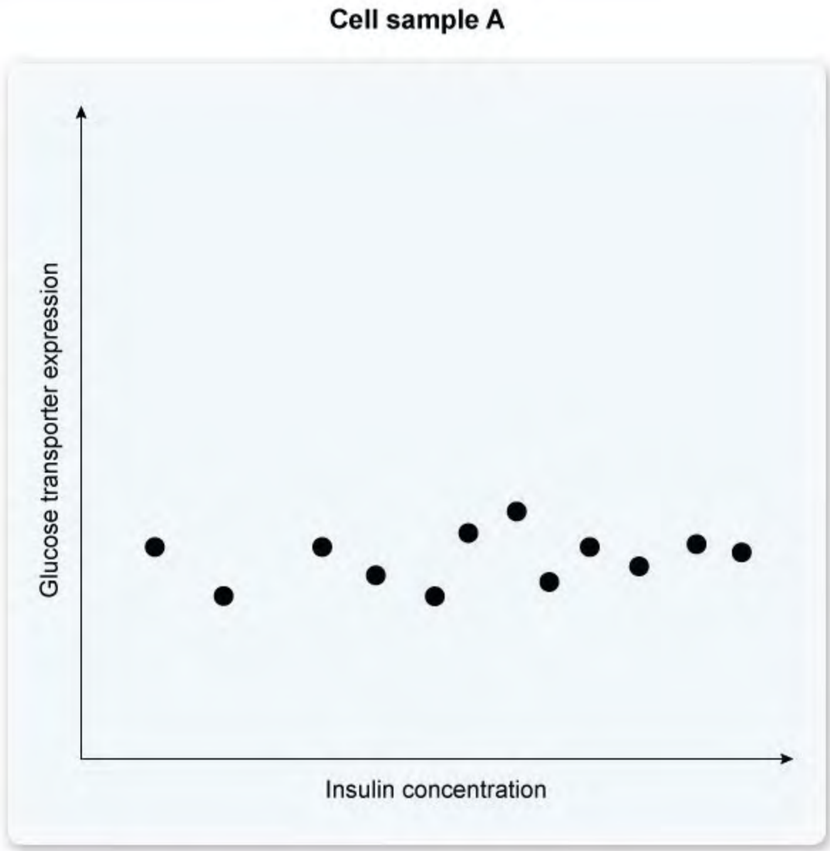
©UWorld

Cell sample B

https://t.me/USMLEWorldStep1

Researchers are investigating the relationship between glucose transport proteins and insulin concentration in
differe
increa
measu

Exhibit Display



©UWorld

Zoom In Zoom Out Reset New | Existing My Notebook

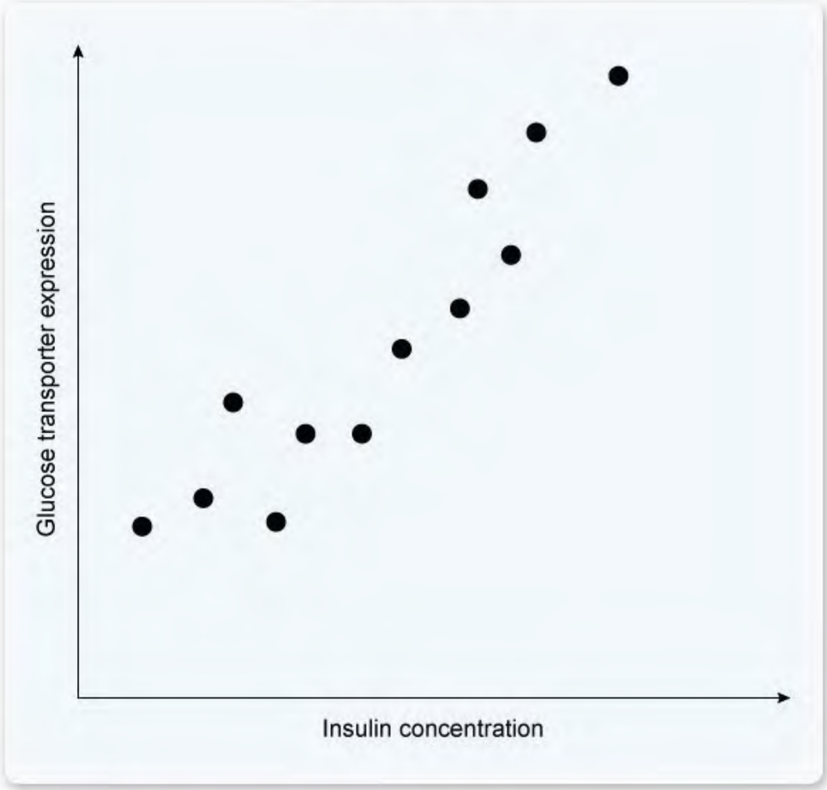
Cell sample B

https://t.me/USMLEWorldStep1

Insulin concentration

Exhibit Display

Cell sample B



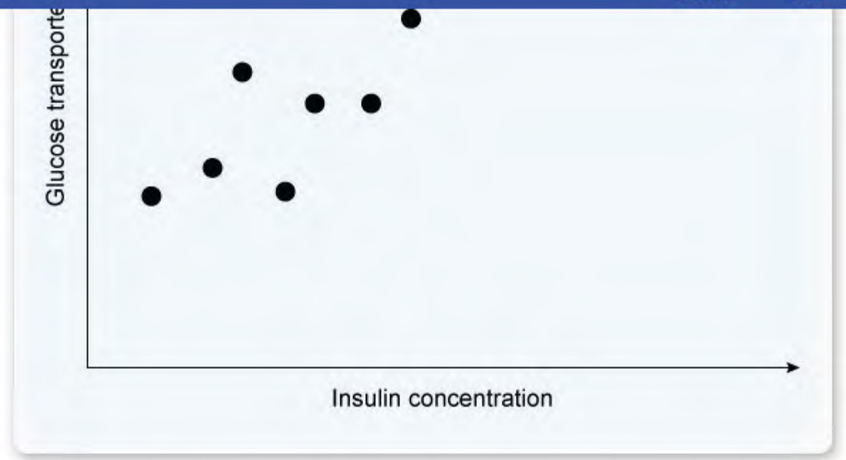
©UWorld

Zoom In Zoom Out Reset New | Existing My Notebook

Which

Cell sample A Cell sample B

https://t.me/USMLEWorldStep1



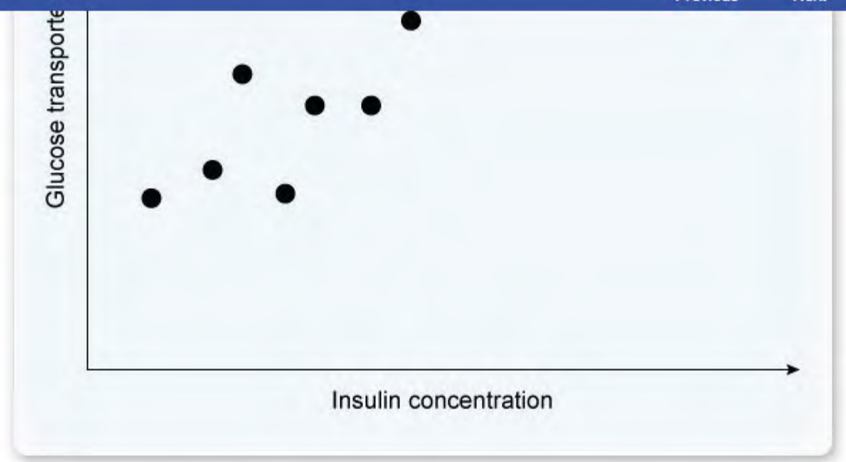
©UWorld

Which of the following cell types are most likely represented in cell samples A and B, respectively?

	Cell sample A	Cell sample B
A.	Cerebral neurons	Hepatocytes
B.	Intestinal epithelial cells	Pancreatic beta cells
C.	Renal tubular cells	Hepatocytes
D.	Renal tubular cells	Skeletal myocytes
E.	Skeletal myocytes	Adipocytes

Submit

https://t.me/USMLEWorldStep1



©UWorld

Which of the following cell types are most likely represented in cell samples A and B, respectively?

	Cell sample A	Cell sample B	
✗ A.	Cerebral neurons	Hepatocytes	(24%)
B.	Intestinal epithelial cells	Pancreatic beta cells	(5%)
C.	Renal tubular cells	Hepatocytes	(9%)
✓ D.	Renal tubular cells	Skeletal myocytes	(54%)
E.	Skeletal myocytes	Adipocytes	(6%)

Incorrect
Correct answer
D

54%
Answered correctly

17 secs
Time Spent

2023
Version

https://t.me/USMLEWorldStep1

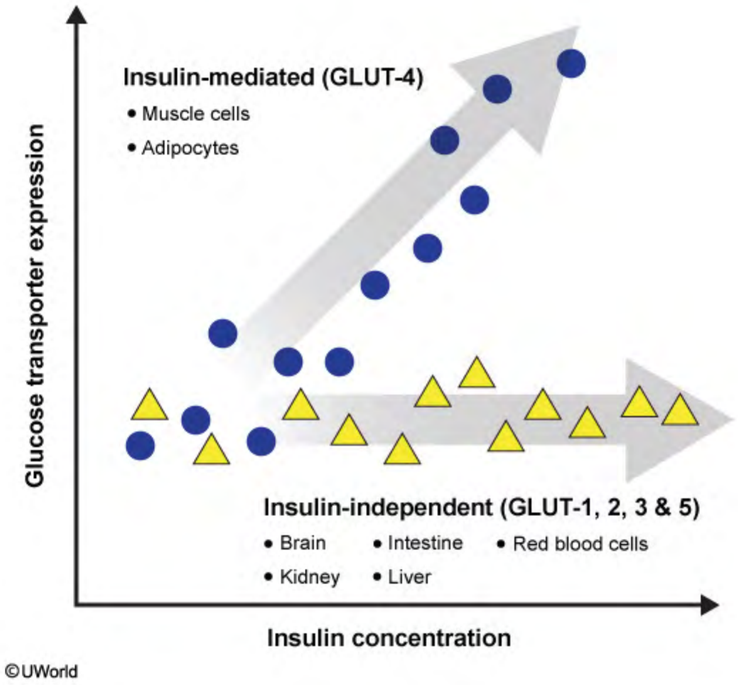
Incorrect
Correct answer
D

54%
Answered correctly

17 secs
Time Spent

2023
Version

Exhibit Display

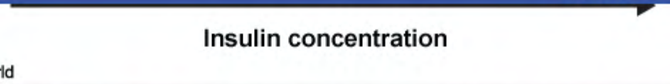


Zoom In Zoom Out Reset New | Existing My Notebook

Expl

The gl
glucos
GLUT-
insulin
the ce
facilitates insulin-mediated glucose uptake and storage.

https://t.me/USMLEWorldStep1



©UWorld

The **glucose transport proteins** (GLUTs) are a family of transmembrane proteins responsible for transport of glucose across cell membranes. Of these, only **GLUT-4** is **responsive to insulin**. In the absence of insulin, GLUT-4 is sequestered in the cytoplasm and the cells become less permeable to glucose. However, increasing insulin concentrations induce translocation of GLUT-4 to the plasma membrane, facilitating glucose transport into the cell (**sample B**). GLUT-4 is predominantly expressed in **skeletal muscle cells and adipocytes**, where it facilitates insulin-mediated glucose uptake and storage.

In contrast to GLUT-4, **GLUTs 1, 2, 3, and 5** are always present on the plasma membrane, regardless of insulin levels, and are responsible for **insulin-independent** glucose transport (**sample A**).

- GLUT-1 contributes to basal glucose transport in erythrocytes and at the blood-brain barrier.
- GLUT-2 is present in hepatocytes, pancreatic beta cells, and at the basolateral membrane of **renal tubules** and small intestinal mucosa. It plays a role in absorption of dietary glucose, reabsorption of glucose from renal tubules, hepatic glucose regulation, and sensitivity of beta cells to circulating glucose.
- GLUT-3 is involved in placental and neuronal glucose transport.
- GLUT-5 is a fructose transporter found in spermatocytes and the gastrointestinal tract.

(Choices A, B, and C) Glucose uptake by hepatocytes, pancreatic beta cells, neurons, and enterocytes primarily involves insulin-independent glucose transporters and does not substantially change with insulin concentration.

(Choice E) Both skeletal myocytes and adipocytes express GLUT-4 and would show increased glucose uptake in response to insulin.

Educational objective:
Glucose transport protein (GLUT)-4 is an insulin-sensitive glucose transporter expressed in skeletal muscle cells and adipocytes that translocates to the plasma membrane in response to increasing insulin levels. In contrast, GLUT-1, 2, 3, and 5 are always present on the plasma membrane and constitutively transport glucose in an insulin-independent manner.

References

https://t.me/USMLEWorldStep1

A 36-year-old man with type 1 diabetes mellitus comes to the office due to recurrent hypoglycemic episodes. He previously had difficulty controlling his high blood glucose levels, but over the past several weeks his blood glucose has intermittently dropped to <50 mg/dL with accompanying symptoms of tremulousness and headache. There have been no recent changes in his diet, activity level, insulin dosage, or other medical therapy. The patient's other medical conditions include chronic kidney disease from diabetic nephropathy. His estimated glomerular filtration rate has declined to 20 mL/min in recent months, and he is under consideration for initiation of hemodialysis. Physical examination findings are unchanged from the previous office visit 3 months ago. Which of the following is most likely contributing to this patient's current glycemic disturbances?

- A. Decreased hepatic glucose production
- B. Decreased renal insulin clearance
- C. Increased pancreatic insulin secretion
- D. Increased renal glucose excretion
- E. Increased tissue insulin sensitivity

Submit

https://t.me/USMLEWorldStep1

A 36-year-old man with type 1 diabetes mellitus comes to the office due to recurrent hypoglycemic episodes. He previously had difficulty controlling his high blood glucose levels, but over the past several weeks his blood glucose has intermittently dropped to <50 mg/dL with accompanying symptoms of tremulousness and headache. There have been no recent changes in his diet, activity level, insulin dosage, or other medical therapy. The patient's other medical conditions include chronic kidney disease from diabetic nephropathy. His estimated glomerular filtration rate has declined to 20 mL/min in recent months, and he is under consideration for initiation of hemodialysis. Physical examination findings are unchanged from the previous office visit 3 months ago. Which of the following is most likely contributing to this patient's current glycemic disturbances?

- A. Decreased hepatic glucose production (4%)
- ✓ B. Decreased renal insulin clearance (59%)
- C. Increased pancreatic insulin secretion (1%)
- D. Increased renal glucose excretion (32%)
- E. Increased tissue insulin sensitivity (1%)

Correct | 59% Answered correctly | 03 secs Time Spent | 2023 Version

Explanation

Insulin is a peptide hormone that has both **renal and hepatic clearance**. Degradation of circulating insulin in the kidneys is dependent on an adequate glomerular filtration rate (GFR), which allows for delivery of insulin to the proximal tubule cells where it is broken down. **Chronic kidney disease** (CKD) causes **decreased GFR**, which impairs insulin clearance.

In patients with normal pancreatic function, hypoglycemia is avoided because pancreatic insulin production decreases and circulating insulin levels rapidly return to baseline. However, patients taking **exogenous insulin**

https://t.me/USMLEWorldStep1

Explanation

Insulin is a peptide hormone that has both **renal and hepatic clearance**. Degradation of circulating insulin in the kidneys is dependent on an adequate glomerular filtration rate (GFR), which allows for delivery of insulin to the proximal tubule cells where it is broken down. **Chronic kidney disease** (CKD) causes **decreased GFR**, which impairs insulin clearance.

In patients with normal pancreatic function, hypoglycemia is avoided because pancreatic insulin production decreases and circulating insulin levels rapidly return to baseline. However, patients taking **exogenous insulin** are at increased **risk of hypoglycemia** if there is no decrease in dosage to compensate for renal failure.

In light of this patient's worsening CKD, his symptomatic hypoglycemia is likely due to **reduced renal insulin clearance** and a prolonged insulin effect.

(Choice A) Advanced CKD leads to reduced gluconeogenesis in the kidney, not the liver. Hepatic gluconeogenesis is inhibited by inflammatory cytokine release (eg, sepsis), heavy alcohol use, and beta blockers.

(Choice C) Patients with type 1 diabetes typically have minimal to no secretory reserve and cannot increase insulin in response to physiologic stimuli.

(Choice D) Increased renal glucose excretion can cause glucosuria; however, this occurs in the setting of significant hyperglycemia (not hypoglycemia). In addition, this patient's low glomerular filtration rate would be expected to reduce renal glucose excretion.

(Choice E) Insulin sensitivity is decreased (not increased) in CKD due to the accumulation of urea and other metabolic toxins.

Educational objective:
Insulin has both renal and hepatic clearance. In patients with advanced chronic kidney disease and diabetes mellitus, decreased renal clearance of insulin can lead to symptomatic hypoglycemia if exogenous insulin doses are not adjusted based on the change in renal function.

References

- Pathophysiology and management of hypoglycemia in end-stage renal disease patients: a review.

https://t.me/USMLEWorldStep1

A 67-year-old woman comes to the office due to polymyalgia rheumatica. She was diagnosed a year ago and has required supraphysiologic doses of prednisone to control her symptoms. The patient has no other medical conditions. She has adequate intake of calcium and vitamin D from her diet and supplements. The patient does not use tobacco or alcohol. Physical examination is unremarkable. Laboratory evaluation shows normal serum creatinine, 25-hydroxyvitamin D, and calcium levels. Bone density measured by dual x-ray absorptiometry (DXA) reveals a significant decline when compared to her bone density measured at age 65. Which of the following is most likely contributing to this patient's bone loss?

- A. Increased activity of osteoprotegerin
- B. Increased levels of insulin-like growth factor-1
- C. Inhibition of osteoblast precursor cell replication and differentiation
- D. Inhibition of receptor activator of nuclear factor kappa B
- E. Suppression of parathyroid hormone release

Submit

https://t.me/USMLEWorldStep1

A 67-year-old woman comes to the office due to polymyalgia rheumatica. She was diagnosed a year ago and has required supraphysiologic doses of prednisone to control her symptoms. The patient has no other medical conditions. She has adequate intake of calcium and vitamin D from her diet and supplements. The patient does not use tobacco or alcohol. Physical examination is unremarkable. Laboratory evaluation shows normal serum creatinine, 25-hydroxyvitamin D, and calcium levels. Bone density measured by dual x-ray absorptiometry (DXA) reveals a significant decline when compared to her bone density measured at age 65. Which of the following is most likely contributing to this patient's bone loss?

- A. Increased activity of osteoprotegerin (7%)
- ✗ B. Increased levels of insulin-like growth factor-1 (2%)
- ✓ C. Inhibition of osteoblast precursor cell replication and differentiation (53%)
- D. Inhibition of receptor activator of nuclear factor kappa B (34%)
- E. Suppression of parathyroid hormone release (2%)

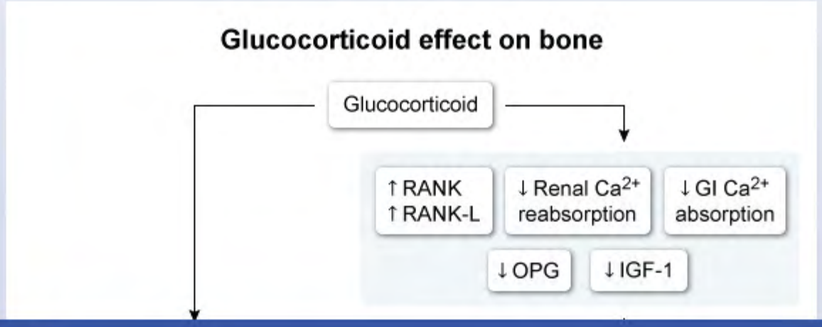
Incorrect
Correct answer
C

53%
Answered correctly

04 secs
Time Spent

2023
Version

Explanation

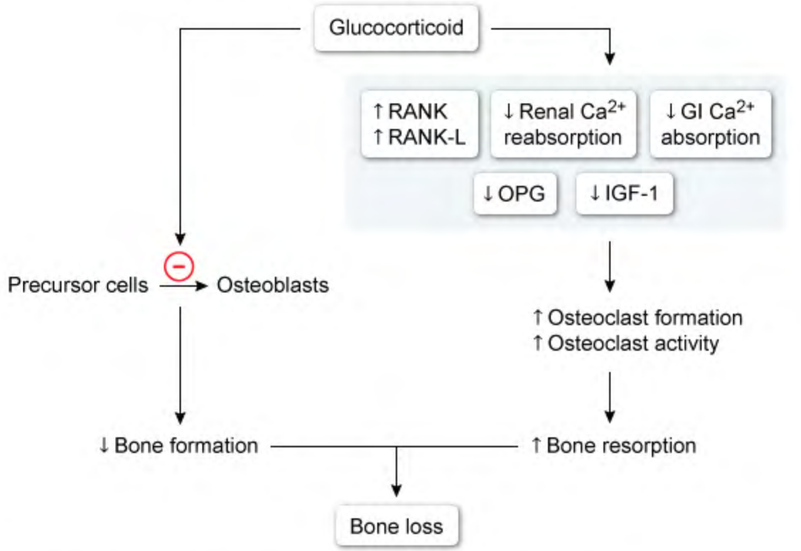


https://t.me/USMLEWorldStep1

A 67-year-old woman comes to the office due to polymyalgia rheumatica. She was diagnosed a year ago and has
require
conditi
not us
creatin
reveal
most li

Exhibit Display

Glucocorticoid effect on bone



GI = gastrointestinal; **IGF-1** = insulin-like growth factor 1; **OPG** = osteoprotegerin; **RANK** = receptor activator of nuclear factor-κB; **RANK-L** = RANK ligand.

©UWorld

Zoom In Zoom Out Reset New | Existing My Notebook

Inco
Corre
C

Expl

↓ OPG ↓ IGF-1

https://t.me/USMLEWorldStep1

RANK = receptor activator of nuclear factor-κB; **RANK-L** = RANK ligand.

©UWorld

Chronic or recurrent **glucocorticoid** (eg, prednisone) use, as is needed in patients with polymyalgia rheumatica, is associated with an increased risk for **osteoporosis**. Glucocorticoids accelerate the development of osteoporosis by a number of mechanisms:

- **Decreased osteoblast effect:** Glucocorticoids **inhibit** the proliferation and differentiation of **osteoblast precursor cells**. They also induce increased rates of apoptosis in mature osteoblasts.
- **Increased osteoclast effect:** Osteoclast differentiation and activity are promoted by the receptor activator of nuclear factor kappa B (RANK)/RANK-ligand; this effect is inhibited by osteoprotegerin, which acts as a decoy receptor. Glucocorticoids increase the expression of RANK and RANK-ligand **(Choice D)** and decrease the expression of osteoprotegerin **(Choice A)**, leading to increased bone resorption.
- **Renal and intestinal calcium wasting:** Glucocorticoids suppress intestinal calcium absorption and renal calcium reabsorption, requiring increased release of calcium from bone to maintain calcium homeostasis.

(Choice B) Insulin-like growth factor-1 (IGF-1) is produced primarily in the liver but also locally in bone. It mediates many of the anabolic effects of growth hormone, including maintenance of bone mass. Glucocorticoids suppress (not increase) levels of IGF-1; in animal models, administration of exogenous IGF-1 mitigates much of the bone loss associated with glucocorticoids.

(Choice E) Glucocorticoids alter the pattern of parathyroid hormone (PTH) secretion (eg, reduced tonic secretion and increased pulsatile PTH secretion), but overall secretion is only minimally changed. In general, bone loss is seen with excessive PTH secretion (ie, hyperparathyroidism) but not suppressed secretion.

Educational objective:
Chronic or recurrent glucocorticoid (eg, prednisone) use can lead to loss of bone density. Glucocorticoids inhibit replication and differentiation of osteoblast precursor cells, increase osteoclast activity, and promote intestinal and renal calcium wasting.

Pharmacology	Endocrine, Diabetes & Metabolism	Osteoporosis
Subject	System	Topic

Copyright © UWorld. All rights reserved.

https://t.me/USMLEWorldStep1

RANK = receptor activator of nuclear factor-κB; **RANK-L** = RANK ligand.

©UWorld

Chroni… **glucocorticoid** (eg, prednisone) use, as is needed in patients with polymyalgia rheumatica, is associ… by a n…

- **D… p…**
- **Ir… n… re… e…**
- **R… c…**

(Choi… media… suppre… the bo…

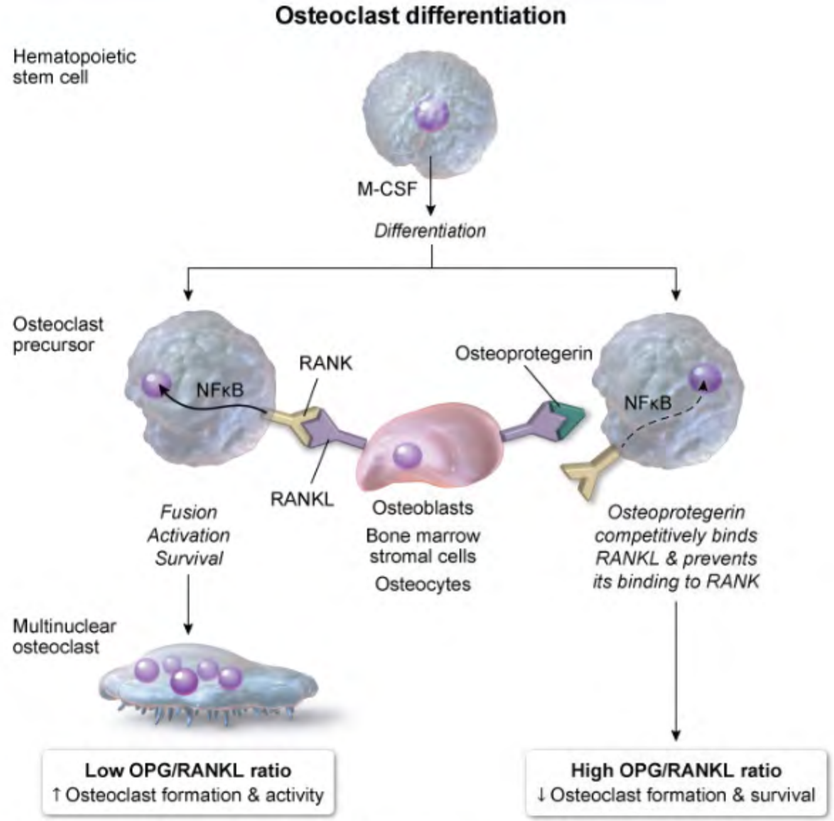
(Choi… and in… seen v…

Educa…
Chron… replica… renal c…

Pharma…
Subject System Topic

Copyright © UWorld. All rights reserved.

Exhibit Display



M-CSF = macrophage colony-stimulating factor; **NFκB** = nuclear factor kappa-light-chain-enhancer of activated B cells; **OPG** = osteoprotegerin; **RANK** = receptor activator of nuclear factor kappa B; **RANKL** = RANK ligand.

©UWorld

Zoom In Zoom Out Reset New | Existing My Notebook

https://t.me/USMLEWorldStep1

A 46-year-old man develops episodes of "dizzy spells" accompanied by palpitations and sweating during exercise. His symptoms improve after drinking orange juice or eating a protein bar. The patient was diagnosed with type 2 diabetes 6 months ago and advised to lose weight with dietary modification and exercise. Since then, he has been working out intensively and has lost 10 kg (22 lb). Which of the following mechanisms is responsible for this patient's symptoms when exercising?

- A. Decreased hepatic glucose production
- B. Increased glucokinase activity
- C. Increased glucose-6-phosphatase activity
- D. Translocation of glucose transporter 2 to the cell membrane
- E. Translocation of glucose transporter 4 to the cell membrane

Submit

https://t.me/USMLEWorldStep1

A 46-year-old man develops episodes of "dizzy spells" accompanied by palpitations and sweating during exercise. His symptoms improve after drinking orange juice or eating a protein bar. The patient was diagnosed with type 2 diabetes 6 months ago and advised to lose weight with dietary modification and exercise. Since then, he has been working out intensively and has lost 10 kg (22 lb). Which of the following mechanisms is responsible for this patient's symptoms when exercising?

- A. Decreased hepatic glucose production (18%)
- ✕ B. Increased glucokinase activity (8%)
- C. Increased glucose-6-phosphatase activity (6%)
- D. Translocation of glucose transporter 2 to the cell membrane (7%)
- ✓ E. Translocation of glucose transporter 4 to the cell membrane (58%)

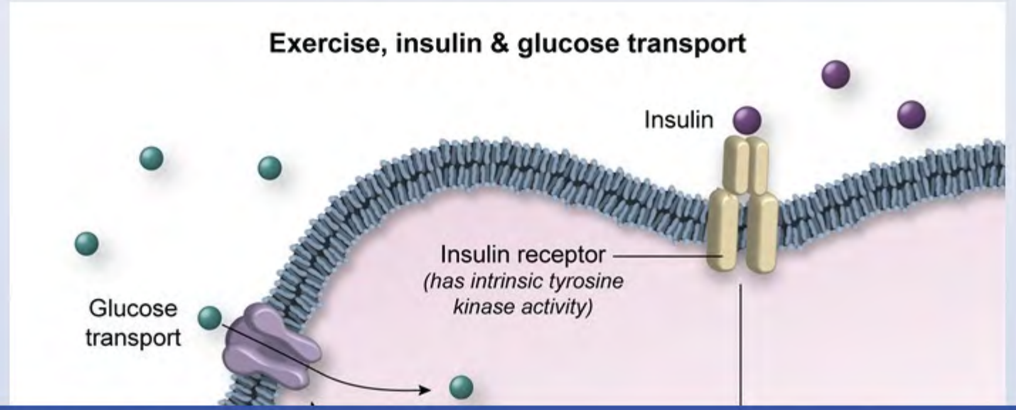
Incorrect
Correct answer
E

58%
Answered correctly

04 secs
Time Spent

2023
Version

Explanation



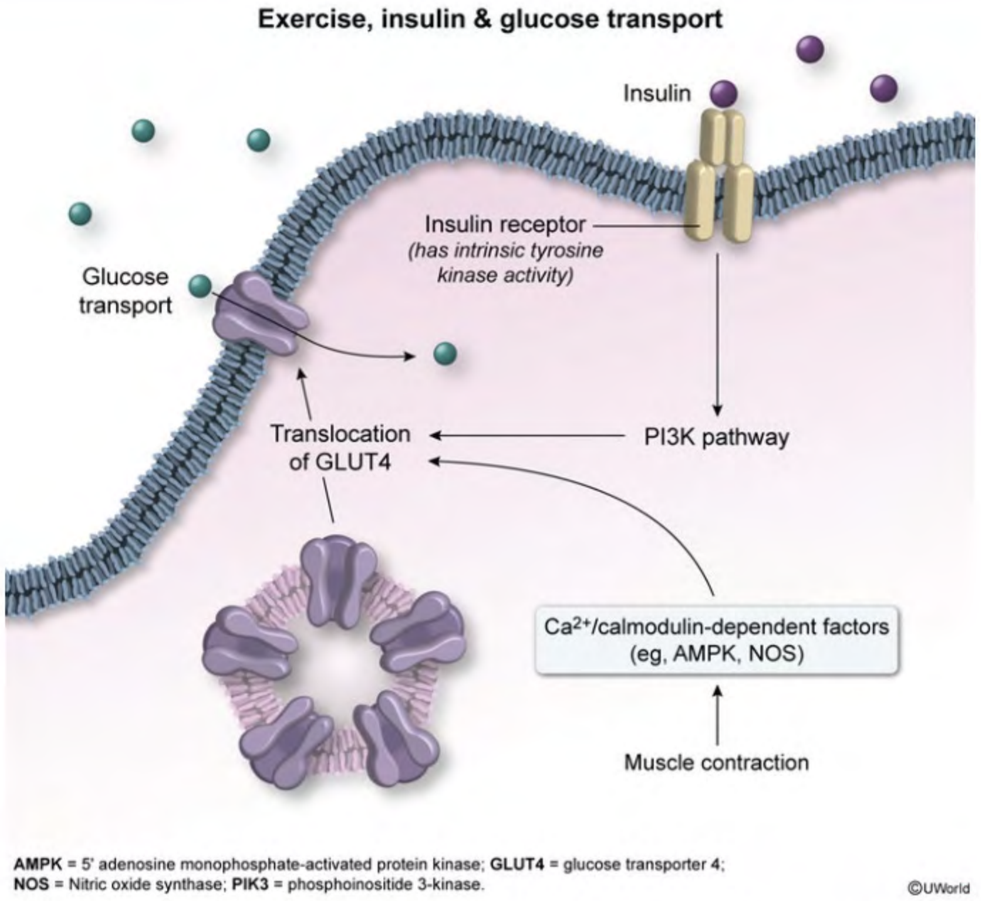
https://t.me/USMLEWorldStep1

A 46-year-old man develops episodes of "dizzy spells" accompanied by palpitations and sweating during exercise.
His sy
diabet
workin
patien

Incc
Corre
E

Expl

Exhibit Display



Zoom In Zoom Out Reset New | Existing My Notebook

https://t.me/USMLEWorldStep1

AMPK = 5' adenosine monophosphate-activated protein kinase; **GLUT4** = glucose transporter 4; **NOS** = Nitric oxide synthase; **PIK3** = phosphoinositide 3-kinase.

©UWorld

Glucose uptake in skeletal muscle occurs by facilitated diffusion via glucose transporter (GLUT) 4. In the fed state, **insulin** induces muscular glucose uptake by stimulating **translocation of GLUT4** from intracellular depots to the plasma membrane and T tubules. As circulating glucose and insulin levels fall in the fasting state, GLUT4 is resequestered, and muscle becomes increasingly dependent on internal stores of glucose and glycogen and, subsequently, on fatty acids released by lipolysis in the liver.

However, translocation of GLUT4 is also induced by **muscle contraction**, allowing insulin-independent **glucose uptake during exercise**. Over time, regular exercise also causes increased expression of GLUT4 and greater insulin-dependent GLUT4 translocation, leading to increased skeletal muscle glucose uptake at any given insulin level (ie, increased insulin sensitivity) and therefore lower blood glucose.

This patient has been engaging in a regular exercise program and is likely experiencing rapid uptake of glucose while exercising. As blood glucose levels fall, counterregulatory factors (eg, glucagon, epinephrine) are activated, leading to his symptoms (eg, palpitations, sweating), which are then relieved by the intake of sugar. **Exercise-induced hypoglycemia** is common in patients with diabetes mellitus due to the lack of physiologic insulin regulation along with insufficient carbohydrate supplementation.

(Choice A) As blood glucose levels fall during fasting or exercise, glucagon and epinephrine stimulate hepatic glycogenolysis and gluconeogenesis, leading to increased (not decreased) glucose production.

(Choice B) Glucokinase phosphorylates glucose to glucose-6-phosphate, primarily for glycogen synthesis. It is expressed mainly in the liver and is stimulated by rising, not falling, glucose levels.

(Choice C) Glucose-6-phosphatase catalyzes the hydrolysis of glucose-6-phosphate to glucose during gluconeogenesis, thereby helping to maintain glucose levels in the fasting state; increased activity would improve hypoglycemic symptoms by increasing circulating glucose levels.

(Choice D) GLUT2 is found primarily in the liver and pancreatic beta cells, where it facilitates insulin-independent glucose uptake. It is not expressed significantly in muscle or translocated in response to muscle contraction.

Educational objective:
Glucose uptake in skeletal muscle occurs primarily via glucose transporter (GLUT) 4. Muscle contraction and

https://t.me/USMLEWorldStep1

the plasma membrane and T tubules. As circulating glucose and insulin levels fall in the fasting state, GLUT4 is resequestered, and muscle becomes increasingly dependent on internal stores of glucose and glycogen and, subsequently, on fatty acids released by lipolysis in the liver.

However, translocation of GLUT4 is also induced by **muscle contraction**, allowing insulin-independent **glucose uptake during exercise**. Over time, regular exercise also causes increased expression of GLUT4 and greater insulin-dependent GLUT4 translocation, leading to increased skeletal muscle glucose uptake at any given insulin level (ie, increased insulin sensitivity) and therefore lower blood glucose.

This patient has been engaging in a regular exercise program and is likely experiencing rapid uptake of glucose while exercising. As blood glucose levels fall, counterregulatory factors (eg, glucagon, epinephrine) are activated, leading to his symptoms (eg, palpitations, sweating), which are then relieved by the intake of sugar. **Exercise-induced hypoglycemia** is common in patients with diabetes mellitus due to the lack of physiologic insulin regulation along with insufficient carbohydrate supplementation.

(Choice A) As blood glucose levels fall during fasting or exercise, glucagon and epinephrine stimulate hepatic glycogenolysis and gluconeogenesis, leading to increased (not decreased) glucose production.

(Choice B) Glucokinase phosphorylates glucose to glucose-6-phosphate, primarily for glycogen synthesis. It is expressed mainly in the liver and is stimulated by rising, not falling, glucose levels.

(Choice C) Glucose-6-phosphatase catalyzes the hydrolysis of glucose-6-phosphate to glucose during gluconeogenesis, thereby helping to maintain glucose levels in the fasting state; increased activity would improve hypoglycemic symptoms by increasing circulating glucose levels.

(Choice D) GLUT2 is found primarily in the liver and pancreatic beta cells, where it facilitates insulin-independent glucose uptake. It is not expressed significantly in muscle or translocated in response to muscle contraction.

Educational objective:
Glucose uptake in skeletal muscle occurs primarily via glucose transporter (GLUT) 4. Muscle contraction and insulin induce translocation of GLUT4 to the cell surface, increasing glucose uptake during exercise and the fed state, respectively. Over time, regular exercise causes increased expression of GLUT4, leading to increased skeletal muscle glucose uptake at any given insulin level and therefore lower blood glucose levels.

https://t.me/USMLEWorldStep1

the plasma membrane and T tubules. As circulating glucose and insulin levels fall in the fasting state, GLUT4 is
reseq
subse

Howe
uptak
insulin
level (

This p
while
leadin
induc
regula

(Choi
glycog

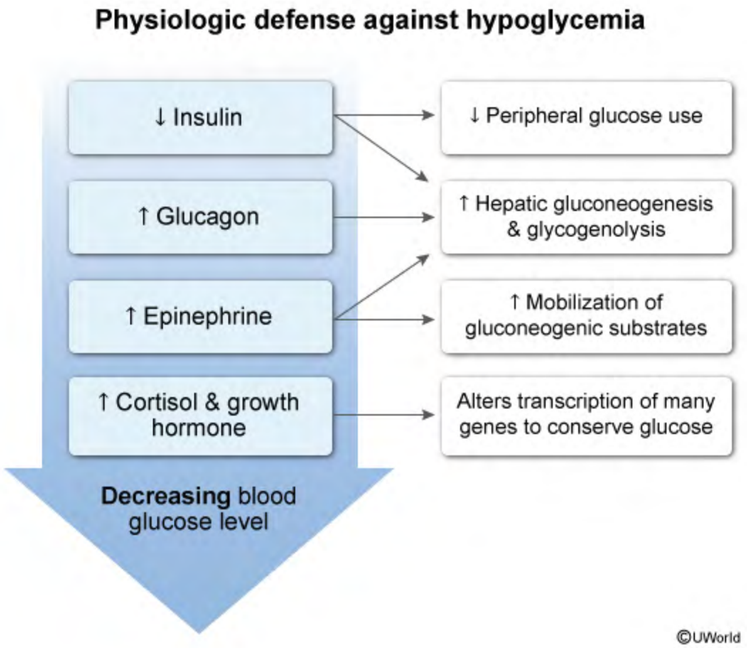
(Choi
expres

(Choi
glucon
hypog

(Choi
glucos

Educa
Glucos
insulin
state,
skeletal muscle glucose uptake at any given insulin level and therefore lower blood glucose levels.

Exhibit Display



Zoom In Zoom Out Reset New | Existing My Notebook

https://t.me/USMLEWorldStep1

A 6-year-old girl is brought to the office for evaluation of short stature. Her parents have noticed that she bears little resemblance to her 2 older siblings. The patient's mother and father are 172.5 cm (5'8") and 183 cm (6') tall, respectively. On physical examination, the patient's height is 3 standard deviations below the mean for her age. Other findings include low-set ears, a high arched palate, a webbed neck, and cubitus valgus. Chromosomal analysis reveals a 45,XO karyotype. The patient is started on a medication to improve growth and normalize her height. Which of the following intracellular pathways is stimulated by the medication used in this patient?

- A. Binding of activated receptors to DNA to modify transcription
- B. Cyclic AMP-Protein kinase A pathway
- C. Diacylglycerol-Protein kinase C pathway
- D. Inositol triphosphate–calcium–calmodulin pathway
- E. JAK-STAT pathway

Submit

https://t.me/USMLEWorldStep1

A 6-year-old girl is brought to the office for evaluation of short stature. Her parents have noticed that she bears little resemblance to her 2 older siblings. The patient's mother and father are 172.5 cm (5'8") and 183 cm (6') tall, respectively. On physical examination, the patient's height is 3 standard deviations below the mean for her age. Other findings include low-set ears, a high arched palate, a webbed neck, and cubitus valgus. Chromosomal analysis reveals a 45,XO karyotype. The patient is started on a medication to improve growth and normalize her height. Which of the following intracellular pathways is stimulated by the medication used in this patient?

- A. Binding of activated receptors to DNA to modify transcription (22%)
- ✗ B. Cyclic AMP-Protein kinase A pathway (13%)
- C. Diacylglycerol-Protein kinase C pathway (3%)
- D. Inositol triphosphate–calcium–calmodulin pathway (5%)
- ✓ E. JAK-STAT pathway (54%)

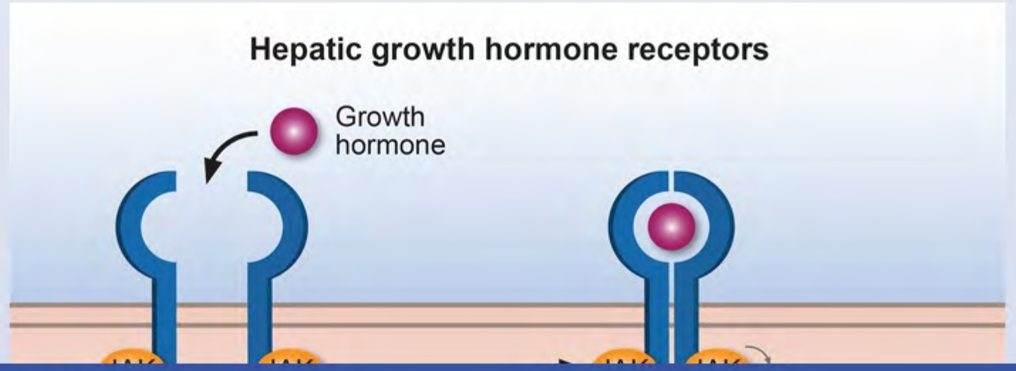
Incorrect
Correct answer
E

54%
Answered correctly

03 secs
Time Spent

2023
Version

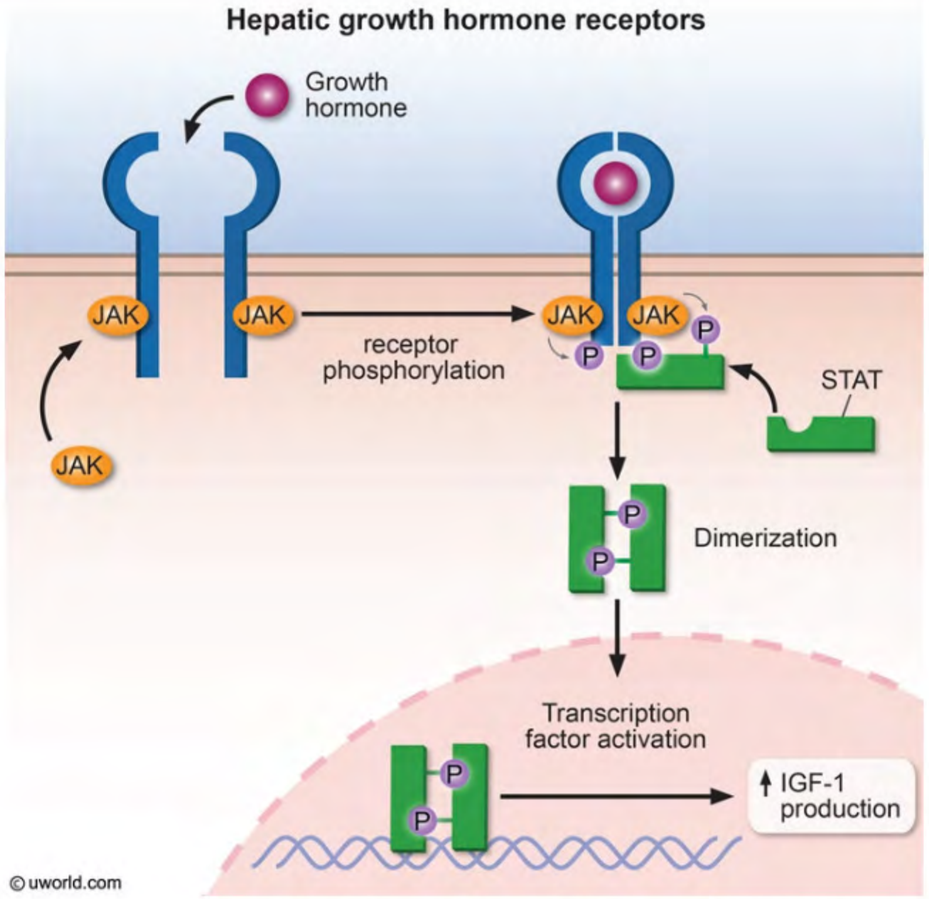
Explanation



https://t.me/USMLEWorldStep1

Expl

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

This patient with a 45,XO karyotype has Turner syndrome. Individuals with this condition are typically treated with growth hormone (GH) when growth failure becomes evident, leading to normalization of height in most patients.

https://t.me/USMLEWorldStep1

This patient with a 45,XO karyotype has Turner syndrome. Individuals with this condition are typically treated with **growth hormone** (GH) when growth failure becomes evident, leading to normalization of height in most patients.

GH promotes growth by acting on the cell surface receptors that stimulate production of insulin-like growth factor-1 (IGF-1), primarily in the liver. One GH molecule binds to 2 receptors on the cell surface, leading to activation of **Janus kinase (JAK)**, a **nonreceptor tyrosine kinase**. JAK subsequently phosphorylates several tyrosine residues in the intracellular domain of the GH receptor. These phosphorylated tyrosine residues function as docking sites for **STAT** (**signal transducer and activator of transcription**). Once STAT is recruited to the receptor, it is also phosphorylated by JAK. STAT then dimerizes and translocates to the nucleus, where it induces *IGF-1* gene transcription by binding to the promoter region. Other molecules that use the JAK-STAT pathway include cytokines (eg, interferon) and hematopoietic growth factors (eg, erythropoietin, G-CSF).

(Choice A) Steroid and thyroid hormones bind to intracellular receptors. Once these receptors are activated, they subsequently bind to the promoter region of target genes to modify transcription.

(Choice B) Several hormones (eg, PTH, ACTH, TSH, ADH [V2 receptor]) activate adenylyl cyclase after binding to G protein-coupled receptors on the cell membrane. Adenylyl cyclase converts ATP to cyclic AMP, which subsequently activates protein kinase A.

(Choices C and D) Various hormones (eg, GnRH, TRH, angiotensin II, ADH [V1 receptor]) function by binding to G protein-coupled receptors that activate phospholipase C. Activated phospholipase C hydrolyzes phosphatidylinositol bisphosphate to inositol triphosphate (IP_3) and diacylglycerol (DAG). IP_3 mobilizes calcium from the endoplasmic reticulum, and DAG directly activates protein kinase C.

Educational objective:
Growth hormone binds to cell surface receptors, leading to intracellular activation of the JAK-STAT pathway. Cytokines (eg, interferon) and hematopoietic growth factors (eg, erythropoietin, G-CSF) also use this pathway.

References

- The role of STAT proteins in growth hormone signaling.

Biochemistry Endocrine, Diabetes & Metabolism Turner syndrome

https://t.me/USMLEWorldStep1

This patient with a 45,XO karyotype has Turner syndrome. Individuals with this condition are typically treated with

growt

GH pr
(IGF-1
Janus
residu
dockin
recept
IGF-1
include

(Choi
subse

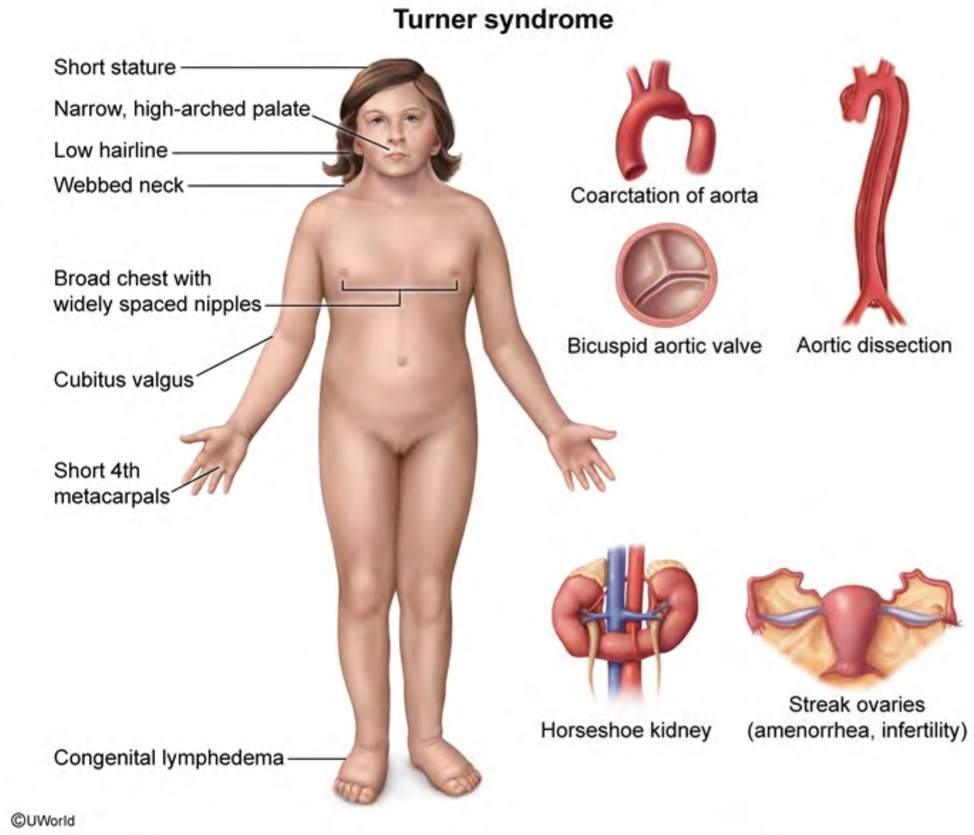
(Choi
G prot
subse

(Choi
G prot
phosp
from t

Educa
Growt
Cytoki

Refere
- The

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Biochemistry | Endocrine, Diabetes & Metabolism | Turner syndrome

https://t.me/USMLEWorldStep1

A 30-year-old man comes to the office with a neck lump. The patient is otherwise asymptomatic and discovered the nodule incidentally while showering. His medical history is significant for a recently diagnosed pheochromocytoma, which was successfully removed. The patient's father died of thyroid cancer in his 30s. An ultrasound reveals a hypoechoic 3-cm nodule in the right lobe of the thyroid gland. Fine-needle biopsy of the nodule is consistent with a subtype of thyroid cancer. The patient undergoes total thyroidectomy with central neck dissection. Which of the following is the most likely histological finding?

- A. Branching structures with interspersed calcified bodies
- B. Follicular hyperplasia with tall cells forming intrafollicular projections
- C. Nests of polygonal cells with Congo red-positive deposits
- D. Pleomorphic giant cell nests with occasional multinucleated cells
- E. Sheets of uniform cells forming small follicles

Submit

https://t.me/USMLEWorldStep1

A 30-year-old man comes to the office with a neck lump. The patient is otherwise asymptomatic and discovered the nodule incidentally while showering. His medical history is significant for a recently diagnosed pheochromocytoma, which was successfully removed. The patient's father died of thyroid cancer in his 30s. An ultrasound reveals a hypoechoic 3-cm nodule in the right lobe of the thyroid gland. Fine-needle biopsy of the nodule is consistent with a subtype of thyroid cancer. The patient undergoes total thyroidectomy with central neck dissection. Which of the following is the most likely histological finding?

- A. Branching structures with interspersed calcified bodies (14%)
- ✗ B. Follicular hyperplasia with tall cells forming intrafollicular projections (16%)
- ✓ C. Nests of polygonal cells with Congo red-positive deposits (49%)
- D. Pleomorphic giant cell nests with occasional multinucleated cells (11%)
- E. Sheets of uniform cells forming small follicles (7%)

Incorrect
Correct answer
C

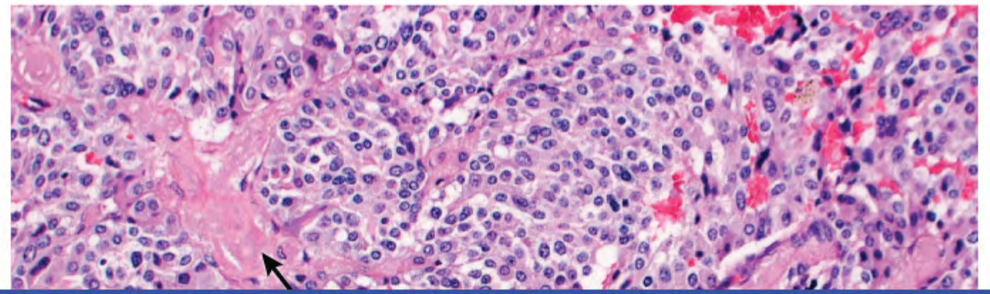
49%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

Medullary thyroid carcinoma



https://t.me/USMLEWorldStep1

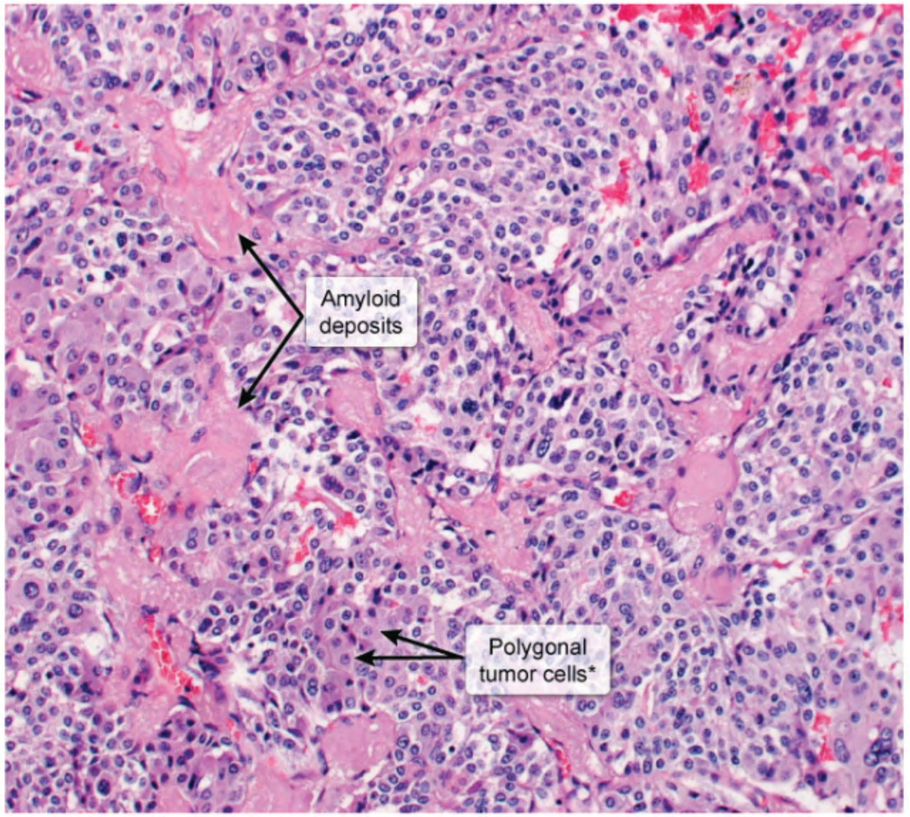
A 30-year-old man comes to the office with a neck lump. The patient is otherwise asymptomatic and discovered
the no
pheoc
ultrasc
nodule
dissec

Incc
Corre
C

Expl

Exhibit Display

Medullary thyroid carcinoma



*Derived from C (parafollicular) cells

©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

This patient has a personal history of pheochromocytoma and a family history of thyroid cancer. His new thyroid malignancy therefore raises suspicion for **multiple endocrine neoplasia type 2** (MEN2), which is characterized by:

- **Medullary thyroid cancer**
- Pheochromocytoma
- Either parathyroid hyperplasia (type 2A) or marfanoid habitus and mucosal neuromas (type 2B)

Approximately 20% of medullary thyroid cancers are familial, occurring as part of MEN2 or familial medullary thyroid cancer syndrome due to germ-line mutations of the RET proto-oncogene. Medullary thyroid cancer is a neuroendocrine tumor that arises from **parafollicular calcitonin-secreting C cells**. Nests or sheets of polygonal or spindle-shaped cells with extracellular **amyloid** deposits are seen microscopically. These amyloid deposits are derived from calcitonin secreted by the neoplastic C cells and stain with **Congo red**. Despite overproduction of calcitonin, hypocalcemia is not a prominent feature.

(Choice A) Gross inspection of papillary thyroid cancer may reveal formation of visible papillae; microscopic inspection of papillae shows a fibrovascular core, often with laminar calcifications (psammoma bodies). The cells contain pale nuclei with finely dispersed chromatin, giving them an empty or ground-glass appearance (Orphan Annie eye nuclei). Intranuclear inclusions and grooves can be seen due to invagination of the nuclear membrane.

(Choice B) Hyperplastic follicles with tall, crowded cells forming intrafollicular projections can be seen in Graves disease, often with hyperactive resorption of colloid leading to scalloping of the colloid edges.

(Choice D) Anaplastic thyroid cancer is an aggressive tumor with a very poor prognosis. It is most common in older patients (age >60). Cytologic features include markedly pleomorphic cells, including irregular giant cells and biphasic spindle cells.

(Choice E) The presence of colloid-containing microfollicles suggests a benign follicular adenoma. Follicular carcinoma can also contain small follicles but will show vascular or capsular invasion.

Educational objective:
Medullary thyroid cancer is a neuroendocrine tumor that arises from parafollicular calcitonin-secreting C cells. It is characterized by nests or sheets of polygonal or spindle-shaped cells with extracellular amyloid deposits derived

https://t.me/USMLEWorldStep1

- **Medullary thyroid cancer**
- Pheochromocytoma
- Either parathyroid hyperplasia (type 2A) or marfanoid habitus and mucosal neuromas (type 2B)

Approximately 20% of medullary thyroid cancers are familial, occurring as part of MEN2 or familial medullary thyroid cancer syndrome due to germ-line mutations of the RET proto-oncogene. Medullary thyroid cancer is a neuroendocrine tumor that arises from **parafollicular calcitonin-secreting C cells**. Nests or sheets of polygonal or spindle-shaped cells with extracellular **amyloid** deposits are seen microscopically. These amyloid deposits are derived from calcitonin secreted by the neoplastic C cells and stain with **Congo red**. Despite overproduction of calcitonin, hypocalcemia is not a prominent feature.

(Choice A) Gross inspection of papillary thyroid cancer may reveal formation of visible papillae; microscopic inspection of papillae shows a fibrovascular core, often with laminar calcifications (psammoma bodies). The cells contain pale nuclei with finely dispersed chromatin, giving them an empty or ground-glass appearance (Orphan Annie eye nuclei). Intranuclear inclusions and grooves can be seen due to invagination of the nuclear membrane.

(Choice B) Hyperplastic follicles with tall, crowded cells forming intrafollicular projections can be seen in Graves disease, often with hyperactive resorption of colloid leading to scalloping of the colloid edges.

(Choice D) Anaplastic thyroid cancer is an aggressive tumor with a very poor prognosis. It is most common in older patients (age >60). Cytologic features include markedly pleomorphic cells, including irregular giant cells and biphasic spindle cells.

(Choice E) The presence of colloid-containing microfollicles suggests a benign follicular adenoma. Follicular carcinoma can also contain small follicles but will show vascular or capsular invasion.

Educational objective:
Medullary thyroid cancer is a neuroendocrine tumor that arises from parafollicular calcitonin-secreting C cells. It is characterized by nests or sheets of polygonal or spindle-shaped cells with extracellular amyloid deposits derived from calcitonin.

Pathology	Endocrine, Diabetes & Metabolism	Thyroid cancer
Subject	System	Topic

https://t.me/USMLEWorldStep1

This patient has a personal history of pheochromocytoma and a family history of thyroid cancer. His new thyroid malign
by:

- M
- P
- E

Appro
thyroid
neuroe
or spir
derive
calcito

(Choi
inspec
contai
Annie

(Choi
diseas

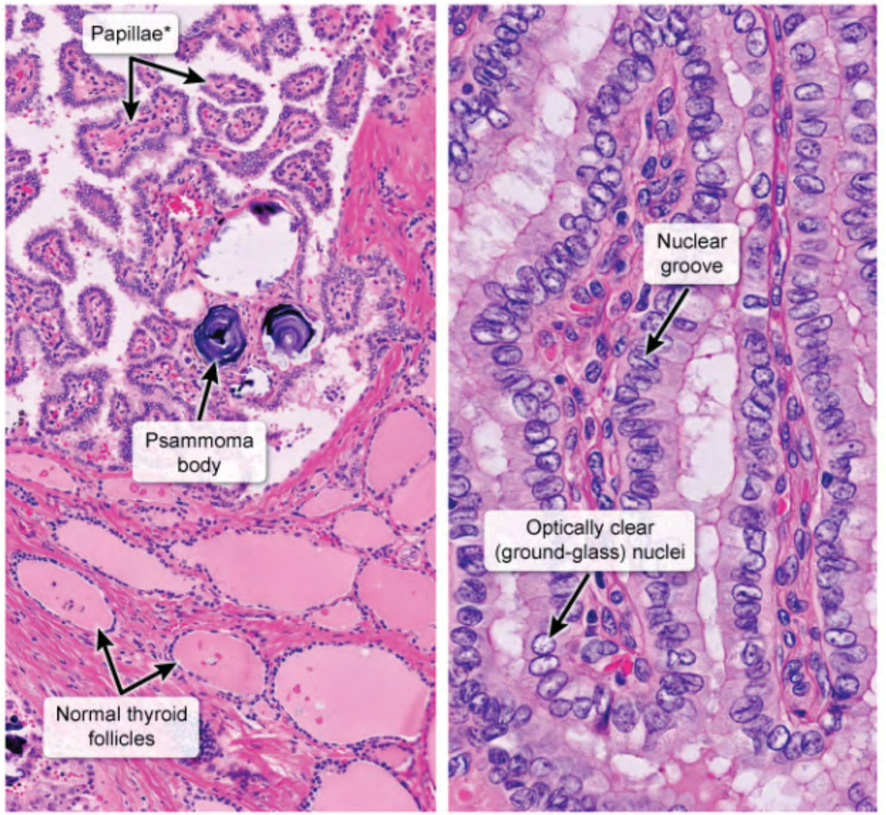
(Choi
older p
biphas

(Choi
carcin

Educa
Medullary thyroid cancer is a neuroendocrine tumor that arises from parafollicular calcitonin-secreting C cells. It is characterized by nests or sheets of polygonal or spindle-shaped cells with extracellular amyloid deposits derived

Exhibit Display

Papillary thyroid carcinoma



*Fibrovascular cores lined by epithelial cells

©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

This patient has a personal history of pheochromocytoma and a family history of thyroid cancer. His new thyroid malign
by:

- M
- P
- E

Appro
thyroi
neuro
or spi
derive
calcito

(Choi
inspec
contai
Annie

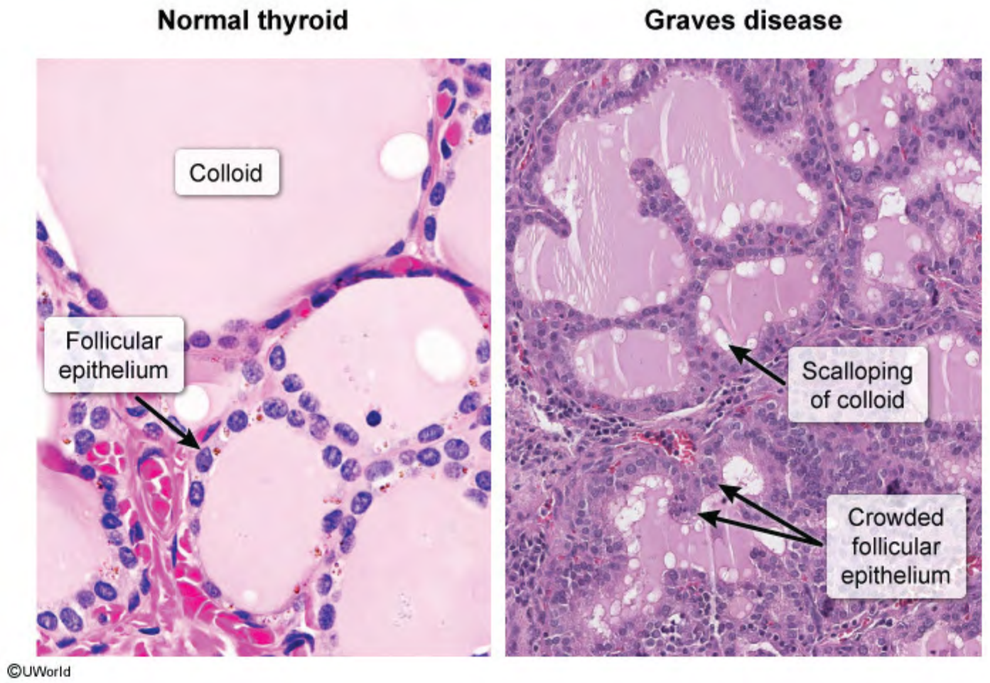
(Choi
diseas

(Choi
older p
biphas

(Choi
carcin

Educa
Medullary thyroid cancer is a neuroendocrine tumor that arises from parafollicular calcitonin-secreting C cells. It is characterized by nests or sheets of polygonal or spindle-shaped cells with extracellular amyloid deposits derived

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

This patient has a personal history of pheochromocytoma and a family history of thyroid cancer. His new thyroid malign
by:

- M
- P
- E

Appro
thyroi
neuro
or spi
derive
calcito

(Choi
inspec
contai
Annie

(Choi
diseas

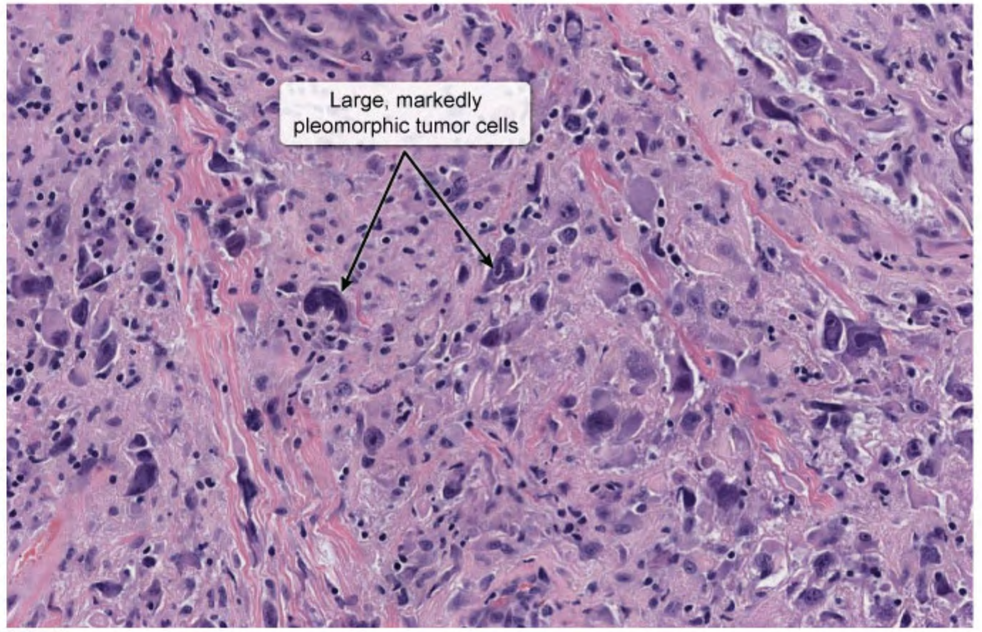
(Choi
older p
biphas

(Choi
carcin

Educa
Medullary thyroid cancer is a neuroendocrine tumor that arises from parafollicular calcitonin-secreting C cells. It is characterized by nests or sheets of polygonal or spindle-shaped cells with extracellular amyloid deposits derived

Exhibit Display

Anaplastic thyroid carcinoma



©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

- **Medullary thyroid cancer**
- P
- E

Approx
thyroid
neuroe
or spir
derive
calcito

(Choi
inspec
contai
Annie

(Choi
diseas

(Choi
older p
biphas

(Choi
carcin

Educa
Medul
charac
from c

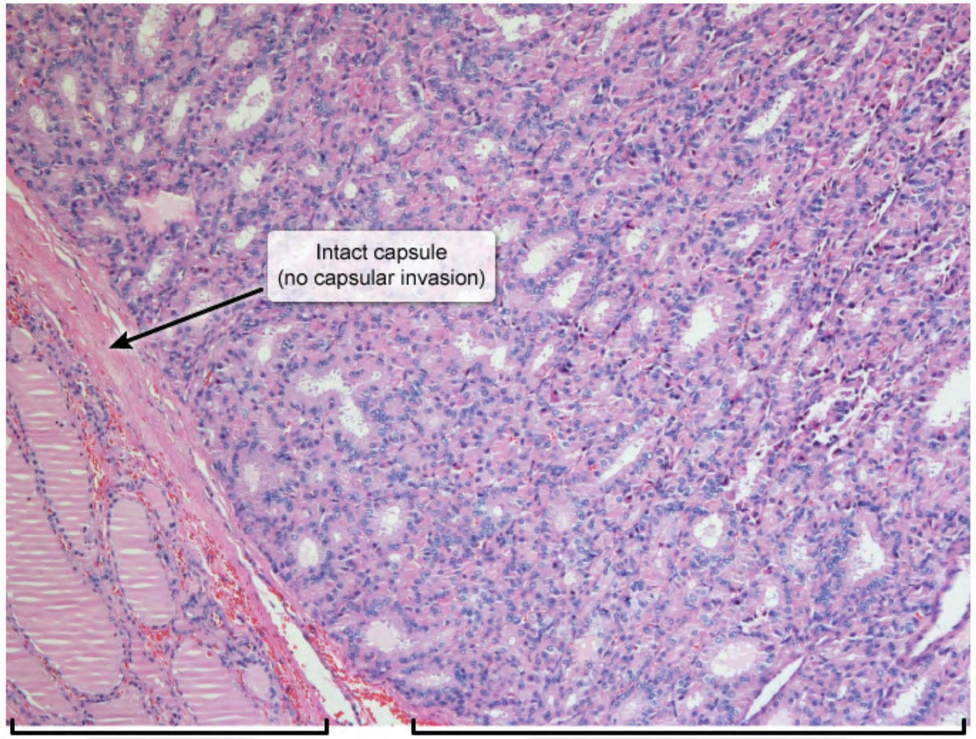
Pathology
Subject

Endocrine, Diabetes & Metabolism
System

Thyroid cancer
Topic

Exhibit Display

Follicular adenoma



©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

A 19-year-old man is brought to the emergency department due to weakness and confusion. Family members report that for the last 2 weeks he has experienced polyuria, polydipsia, and increased appetite. Medical history is remarkable for an appendectomy at age 12. The patient does not use tobacco, alcohol, or illicit drugs. Family history is significant for hypothyroidism in his brother. Temperature is 36.7 C (98 F), blood pressure is 90/60 mm Hg, pulse is 97/min, and respirations are 22/min. On physical examination, the patient is lethargic but follows simple commands. His breath has a fruity odor. This patient is most likely deficient in a hormone that normally performs which of the following actions?

- A. Activates hormone-sensitive lipase
- B. Decreases glucagon secretion
- C. Decreases muscle glycogen synthesis
- D. Increases hepatic glucose production
- E. Increases renal glucose reabsorption

Submit

https://t.me/USMLEWorldStep1

A 19-year-old man is brought to the emergency department due to weakness and confusion. Family members report that for the last 2 weeks he has experienced polyuria, polydipsia, and increased appetite. Medical history is remarkable for an appendectomy at age 12. The patient does not use tobacco, alcohol, or illicit drugs. Family history is significant for hypothyroidism in his brother. Temperature is 36.7 C (98 F), blood pressure is 90/60 mm Hg, pulse is 97/min, and respirations are 22/min. On physical examination, the patient is lethargic but follows simple commands. His breath has a fruity odor. This patient is most likely deficient in a hormone that normally performs which of the following actions?

- A. Activates hormone-sensitive lipase (10%)
- ✓ B. Decreases glucagon secretion (74%)
- C. Decreases muscle glycogen synthesis (3%)
- D. Increases hepatic glucose production (8%)
- E. Increases renal glucose reabsorption (3%)

Correct | 74% Answered correctly | 03 secs Time Spent | 2023 Version

Explanation

Insulin effects		
Effect	**Target organs**	**Consequences of inadequate insulin**
↑ Glucose uptake	• Skeletal muscle • Adipose tissue • Liver	• **Hyperglycemia** ◦ Polyuria, polydipsia ◦ Lethargy
↑ Glycogen synthesis/		

https://t.me/USMLEWorldStep1

Insulin effects		
Effect	**Target organs**	**Consequences of inadequate insulin**
↑ Glucose uptake	• Skeletal muscle • Adipose tissue • Liver	• **Hyperglycemia** ○ Polyuria, polydipsia ○ Lethargy ○ Polyphagia or anorexia
↑ Glycogen synthesis/ ↓ glycogenolysis	• Liver	
↓ Glucagon secretion	• Pancreas (alpha cells)	
↓ Lipolysis/ ↓ ketogenesis	• Adipose tissue • Liver	• Ketosis/ketoacidosis
↑ Protein synthesis	• Muscle	• Muscle wasting, weight loss

This patient has undiagnosed type 1 diabetes mellitus and is now presenting with **diabetic ketoacidosis** (polyuria, polydipsia, altered mental status, fruity breath [exhaled ketones]). Diabetic ketoacidosis results from a **deficiency of insulin** coupled with an excess of counterregulatory hormones (ie, glucagon, epinephrine).

Blood glucose levels are normally maintained within a tight range by the opposing effects of insulin (secreted by beta cells) and glucagon (secreted by alpha cells). In the fasting state, low blood glucose levels stimulate secretion of glucagon, which increases blood glucose levels by upregulating glycogenolysis and gluconeogenesis in the liver. In contrast, insulin is released in response to high glucose levels and functions to decrease hepatic glucose production **(Choice D)** and increase glucose uptake by insulin-responsive tissues. **Insulin** also **suppresses glucagon** by directly acting on the alpha cells, enhancing the metabolic effects of insulin.

In type 1 diabetes mellitus, unsuppressed glucagon secretion due to insulin deficiency contributes to excess blood glucose levels.

(Choice A) In adipose tissue, hormone-sensitive lipase hydrolyzes intracellular triglycerides to release free fatty

https://t.me/USMLEWorldStep1

polydipsia, altered mental status, fruity breath [exhaled ketones]). Diabetic ketoacidosis results from a **deficiency of insulin** coupled with an excess of counterregulatory hormones (ie, glucagon, epinephrine).

Blood glucose levels are normally maintained within a tight range by the opposing effects of insulin (secreted by beta cells) and glucagon (secreted by alpha cells). In the fasting state, low blood glucose levels stimulate secretion of glucagon, which increases blood glucose levels by upregulating glycogenolysis and gluconeogenesis in the liver. In contrast, insulin is released in response to high glucose levels and functions to decrease hepatic glucose production **(Choice D)** and increase glucose uptake by insulin-responsive tissues. **Insulin** also **suppresses glucagon** by directly acting on the alpha cells, enhancing the metabolic effects of insulin.

In type 1 diabetes mellitus, unsuppressed glucagon secretion due to insulin deficiency contributes to excess blood glucose levels.

(Choice A) In adipose tissue, hormone-sensitive lipase hydrolyzes intracellular triglycerides to release free fatty acids. Hormone-sensitive lipase is activated by ACTH and epinephrine in the fasting state and is downregulated by insulin in the fed state. In untreated type 1 diabetes, the lack of insulin induces a catabolic state, resulting in increased lipolysis; patients typically lose weight despite a normal or increased appetite.

(Choice C) In skeletal muscle, insulin increases glucose uptake and synthesis of glycogen, which is then available for energy production during exercise. Insulin also increases amino acid transport and ribosomal translation efficiency in muscle tissue, leading to an overall increase in protein synthesis. Insulin deficiency in type 1 diabetes leads to decreased muscle glycogen synthesis and muscle wasting.

(Choice E) In the renal tubules, glucose is actively taken up from the tubular lumen by sodium-glucose co-transporter 2 (SGLT2) and then passed across the basolateral membrane. This occurs independent of insulin levels and leads to near-complete reabsorption of filtered glucose (unless severe hyperglycemia overwhelms the reabsorptive capacity, leading to osmotic diuresis and polyuria).

Educational objective:
Normal blood glucose levels are maintained by the opposing effects of insulin and glucagon. Glucagon stimulates hepatic glycogenolysis and gluconeogenesis, whereas insulin increases peripheral glucose uptake and inhibits lipolysis and ketoacid formation. Insulin also suppresses glucagon release.

References

https://t.me/USMLEWorldStep1

A 45-year-old woman comes to the office for follow-up of type 2 diabetes mellitus. The patient is taking the maximum dose of metformin. Despite adherence to medications and lifestyle changes, her hemoglobin A1c is 7.7%. Family history is significant for an osteoporotic fracture in her mother. Blood pressure is 134/86 mm Hg, and pulse is 72/min. BMI is 33 kg/m^2. Physical examination shows no abnormalities. The results of other laboratory tests are normal. After discussion, a sodium-glucose cotransporter-2 inhibitor is added to the patient's drug regimen. Which of the following is the most likely additional effect of the newly prescribed medication?

- A. Decreased blood pressure
- B. Increased bone mineral density
- C. Increased fluid retention
- D. Increased postprandial satiety
- E. Increased risk for fasting hypoglycemia

Submit

https://t.me/USMLEWorldStep1

A 45-year-old woman comes to the office for follow-up of type 2 diabetes mellitus. The patient is taking the maximum dose of metformin. Despite adherence to medications and lifestyle changes, her hemoglobin A1c is 7.7%. Family history is significant for an osteoporotic fracture in her mother. Blood pressure is 134/86 mm Hg, and pulse is 72/min. BMI is 33 kg/m^2. Physical examination shows no abnormalities. The results of other laboratory tests are normal. After discussion, a sodium-glucose cotransporter-2 inhibitor is added to the patient's drug regimen. Which of the following is the most likely additional effect of the newly prescribed medication?

- ✓ A. Decreased blood pressure (60%)
- B. Increased bone mineral density (3%)
- ✗ C. Increased fluid retention (9%)
- D. Increased postprandial satiety (8%)
- E. Increased risk for fasting hypoglycemia (18%)

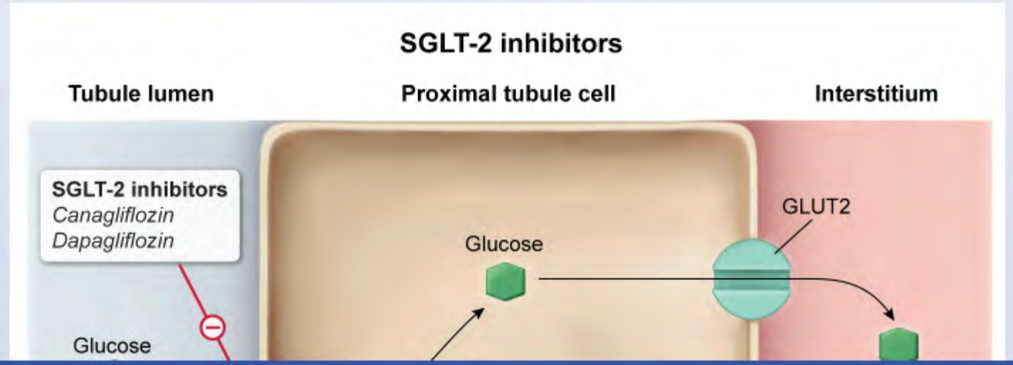
Incorrect
Correct answer
A

60%
Answered correctly

03 secs
Time Spent

2023
Version

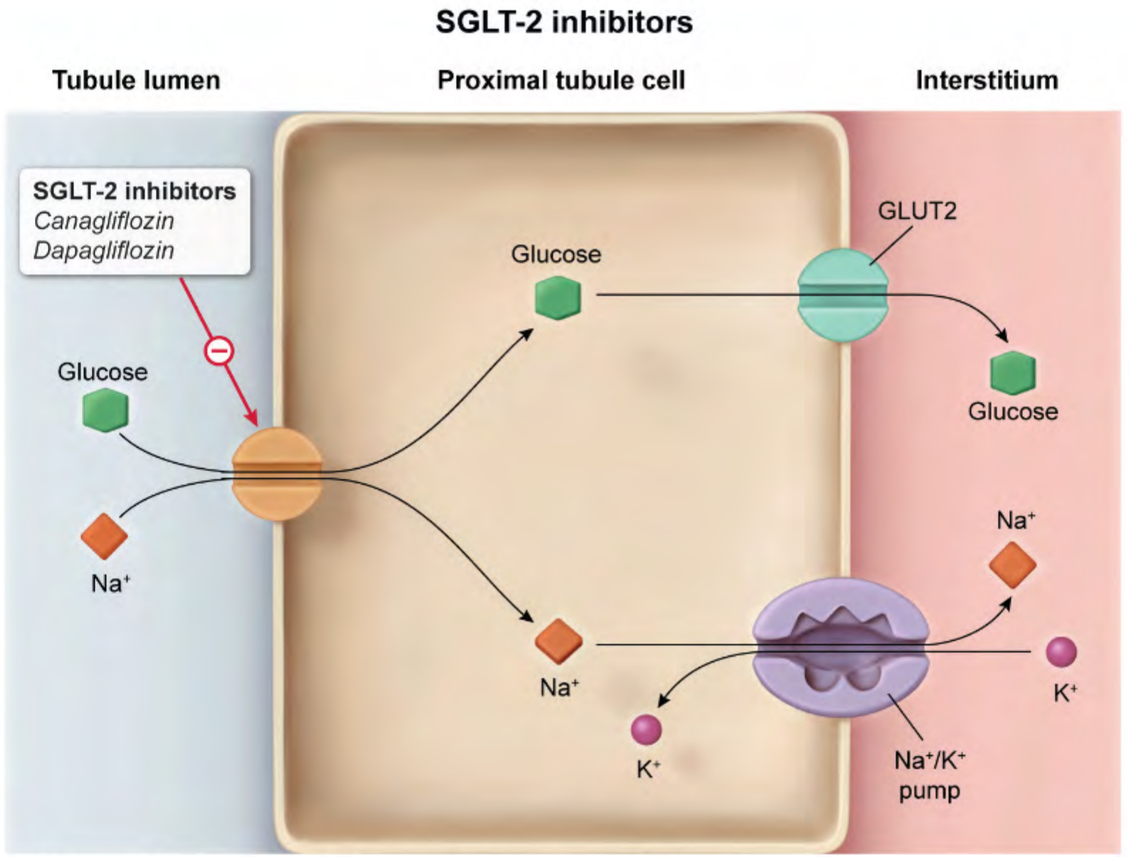
Explanation



https://t.me/USMLEWorldStep1

A 45-year-old woman comes to the office for follow-up of type 2 diabetes mellitus. The patient is taking the maxim
7.7%.
and pu
labora
drug re

Exhibit Display



GLUT2 = glucose transporter 2; **SGLT-2** = sodium-glucose cotransporter 2.

©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1



GLUT2 = glucose transporter 2; **SGLT-2** = sodium-glucose cotransporter 2. ©UWorld

Sodium-glucose cotransporter-2 (SGLT-2) is a transport protein that reabsorbs 90% of filtered glucose in the proximal renal tubule. **SGLT-2 inhibitors** (eg, canagliflozin, dapagliflozin) are oral antidiabetic agents that **decrease renal reabsorption of glucose and sodium**, lowering blood glucose and causing **osmotic diuresis**. Because of their diuretic effects, SGLT-2 inhibitors consequently:

- **decrease blood pressure** (due to intravascular volume reduction)
- lower mortality for **heart failure** (due to preload/afterload reduction)
- slow progression of **diabetic nephropathy** (due to natriuresis, which reduces glomerular hyperfiltration)

In elderly patients taking diuretics (eg, furosemide) and antihypertensives, SGLT-2 inhibitors should be used with caution due to concern for **orthostatic hypotension**, which can lead to falls and acute kidney injury. Because of increased renal glucose excretion, patients typically experience a mild reduction in weight (often desirable) but may be at increased risk for genitourinary infections (eg, vaginal candidiasis).

(Choice B) SGLT-2 inhibitors may decrease (not increase) bone density, possibly because decreased sodium reabsorption is associated with increased phosphate reabsorption in the proximal tubule, resulting in increased parathyroid hormone secretion and, subsequently, increased bone resorption.

(Choice C) Thiazolidinediones (eg, pioglitazone) are antidiabetic medications associated with fluid retention. In contrast, SGLT-2 inhibitors induce a net loss of sodium and fluid.

(Choice D) Glucagon-like peptide-1 (GLP-1) regulates glucose by slowing gastric emptying and increasing glucose-dependent insulin release. Pharmacologic GLP-1 agonists (eg, exenatide) increase postprandial satiety, which leads to weight loss, and are used in the treatment of type 2 diabetes mellitus.

(Choice E) Because renal glucose filtration is proportional to blood glucose level (eg, less glucose is filtered if serum glucose is normal or low, such as in a fasting state), SGLT-2 inhibitors carry a low risk for hypoglycemia. In addition, they do not increase pancreatic insulin secretion, further reducing the risk for hypoglycemia.

Educational objective:
Sodium-glucose cotransporter-2 inhibitors (eg, canagliflozin, dapagliflozin) decrease renal reabsorption of glucose

https://t.me/USMLEWorldStep1

proximal renal tubule. **SGLT-2 inhibitors** (eg, canagliflozin, dapagliflozin) are oral antidiabetic agents that **decrease renal reabsorption of glucose and sodium**, lowering blood glucose and causing **osmotic diuresis**. Because of their diuretic effects, SGLT-2 inhibitors consequently:

- **decrease blood pressure** (due to intravascular volume reduction)
- lower mortality for **heart failure** (due to preload/afterload reduction)
- slow progression of **diabetic nephropathy** (due to natriuresis, which reduces glomerular hyperfiltration)

In elderly patients taking diuretics (eg, furosemide) and antihypertensives, SGLT-2 inhibitors should be used with caution due to concern for **orthostatic hypotension**, which can lead to falls and acute kidney injury. Because of increased renal glucose excretion, patients typically experience a mild reduction in weight (often desirable) but may be at increased risk for genitourinary infections (eg, vaginal candidiasis).

(Choice B) SGLT-2 inhibitors may decrease (not increase) bone density, possibly because decreased sodium reabsorption is associated with increased phosphate reabsorption in the proximal tubule, resulting in increased parathyroid hormone secretion and, subsequently, increased bone resorption.

(Choice C) Thiazolidinediones (eg, pioglitazone) are antidiabetic medications associated with fluid retention. In contrast, SGLT-2 inhibitors induce a net loss of sodium and fluid.

(Choice D) Glucagon-like peptide-1 (GLP-1) regulates glucose by slowing gastric emptying and increasing glucose-dependent insulin release. Pharmacologic GLP-1 agonists (eg, exenatide) increase postprandial satiety, which leads to weight loss, and are used in the treatment of type 2 diabetes mellitus.

(Choice E) Because renal glucose filtration is proportional to blood glucose level (eg, less glucose is filtered if serum glucose is normal or low, such as in a fasting state), SGLT-2 inhibitors carry a low risk for hypoglycemia. In addition, they do not increase pancreatic insulin secretion, further reducing the risk for hypoglycemia.

Educational objective:
Sodium-glucose cotransporter-2 inhibitors (eg, canagliflozin, dapagliflozin) decrease renal reabsorption of glucose and sodium. The resultant osmotic diuresis and natriuresis lead to reduced blood pressure, decreased mortality in heart failure, and slowed progression of diabetic nephropathy.

References

https://t.me/USMLEWorldStep1

proximal renal tubule. **SGLT-2 inhibitors** (eg, canagliflozin, dapagliflozin) are oral antidiabetic agents that **decrea**

Becau

- **d**
- lo
- sl

In elde
caution
increa
be at i

(Choi
reabso
parath

(Choi
contra

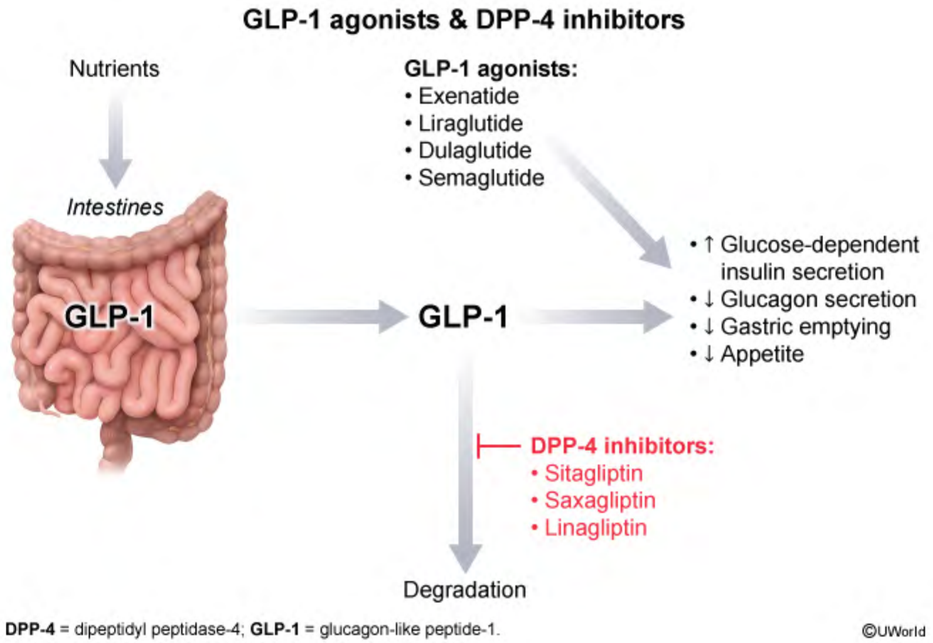
(Choi
glucos
which

(Choi
serum
additio

Educa
Sodiu
and so
heart failure, and slowed progression of diabetic nephropathy.

References

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

A cross-section of the right coronary artery of a 34-year-old Caucasian male who died in the cardiac intensive care unit is shown on the slide below.

His father died of a heart attack at the age of 40. Assuming this patient's disease had a genetic basis, poor receptor expression in which of the following organs is most likely responsible for his condition?

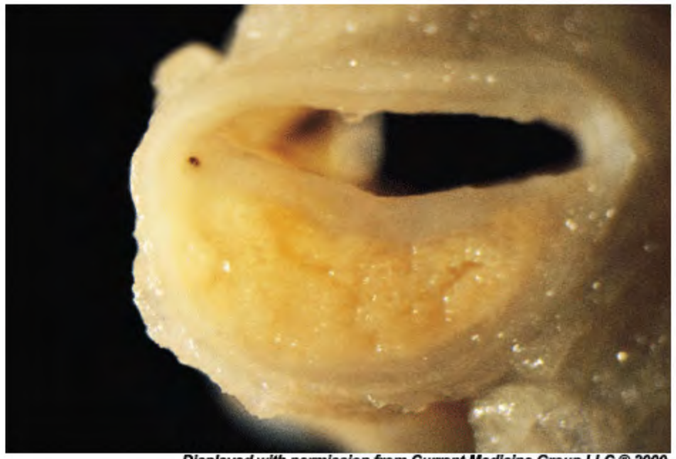
- A. Small intestine
- B. Kidney
- C. Liver
- D. Heart
- E. Lung
- F. Pancreas

Submit

https://t.me/USMLEWorldStep1

A cross-section of the right coronary artery of a 34-year-old Caucasian male who died in the cardiac intensive care unit is

Exhibit Display



Displayed with permission from Current Medicine Group LLC © 2000.

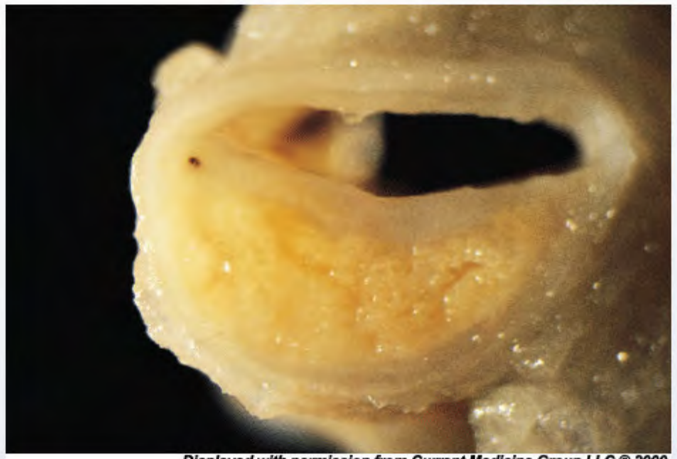
Zoom In Zoom Out Reset New | Existing My Notebook

His fat
recept

Sub

https://t.me/USMLEWorldStep1

A cross-section of the right coronary artery of a 34-year-old Caucasian male who died in the cardiac intensive care unit is shown on the slide below.



Displayed with permission from Current Medicine Group LLC © 2000.

His father died of a heart attack at the age of 40. Assuming this patient's disease had a genetic basis, poor receptor expression in which of the following organs is most likely responsible for his condition?

- A. Small intestine (3%)
- ✗ B. Kidney (2%)
- ✓ C. Liver (87%)
- D. Heart (3%)
- E. Lung (1%)
- F. Pancreas (2%)

Incorrect
Correct answer
C

87%
Answered correctly

08 secs
Time Spent

2023
Version

https://t.me/USMLEWorldStep1

Explanation

This patient's right coronary artery (RCA) shows significant occlusion by a large atheromatous plaque with a soft, yellow, lipid core composed mainly of cholesterol and cholesterol esters. Presumably, this patient died from a complication of advanced atherosclerosis, such as a myocardial infarction. His father's similar fate at a young age suggests a familial condition, most likely familial hypercholesterolemia. Familial hypercholesterolemia is one of the most common inherited disorders, and results from autosomal dominant mutations of the LDL receptor gene.

The liver LDL receptor is normally the greatest contributor to the removal of cholesterol-containing IDL and LDL particles from the circulation. Although numerous other cell types, including smooth muscle cells, adrenocortical cells, fibroblasts, and lymphocytes also express high-affinity LDL receptors, approximately 70% of the plasma LDL is normally cleared by the liver. Heterozygotes with one mutant LDL receptor gene have a 2- to 3-fold elevation of plasma cholesterol from birth, due to reduced hepatic IDL and LDL uptake. Homozygotes may have a 5- to 6-fold elevation. In both heterozygotes and homozygotes, the progression of atherosclerosis with aging is accelerated. Complications include coronary artery disease at an unusually young age, as was the case for the patient in the vignette.

(Choices A, B, D, E and F) Although many cell types express the LDL receptor, their rate of LDL uptake from the circulation is usually less than that of hepatocytes. The liver is also the major site of cholesterol catabolism and excretion, making it the most important organ in serum cholesterol level homeostasis.

Educational Objective:
Familial hypercholesterolemia, one of the most common autosomal dominant disorders, is the result of heterozygous or homozygous LDL receptor gene mutations, which cause hepatocyte under-expression of functional LDL receptors. This condition can lead to accelerated atherosclerosis and early-onset coronary artery disease.

Pathology	Endocrine, Diabetes & Metabolism	Atherosclerosis
Subject	System	Topic

Copyright © UWorld. All rights reserved.

https://t.me/USMLEWorldStep1

A 56-year-old man is evaluated for progressive visual impairment. The patient works as part of the grounds crew at an airport, and says he has trouble identifying aircraft at a distance and with filling out paperwork at the end of his shift. His medical history includes poorly controlled diabetes mellitus, hypertension, and gout. A year ago, the patient underwent an uncomplicated repair of a right inguinal hernia. Physical examination shows bilateral clouding of the lens. The remainder of the examination is unremarkable. Which of the following metabolic conversions is most likely contributing to this patient's current condition?

- A. Galactitol to tagatose
- B. Galactose to galactitol
- C. Glucose to sorbitol
- D. Glucose-6-phosphate to 6-phosphogluconolactone
- E. Pyruvate to lactate

Submit

https://t.me/USMLEWorldStep1

A 56-year-old man is evaluated for progressive visual impairment. The patient works as part of the grounds crew at an airport, and says he has trouble identifying aircraft at a distance and with filling out paperwork at the end of his shift. His medical history includes poorly controlled diabetes mellitus, hypertension, and gout. A year ago, the patient underwent an uncomplicated repair of a right inguinal hernia. Physical examination shows bilateral clouding of the lens. The remainder of the examination is unremarkable. Which of the following metabolic conversions is most likely contributing to this patient's current condition?

- A. Galactitol to tagatose (0%)
- ✗ B. Galactose to galactitol (12%)
- ✓ C. Galactose to sorbitol (83%)
- D. Glucose-6-phosphate to 6-phosphogluconolactone (1%)
- E. Pyruvate to lactate (1%)

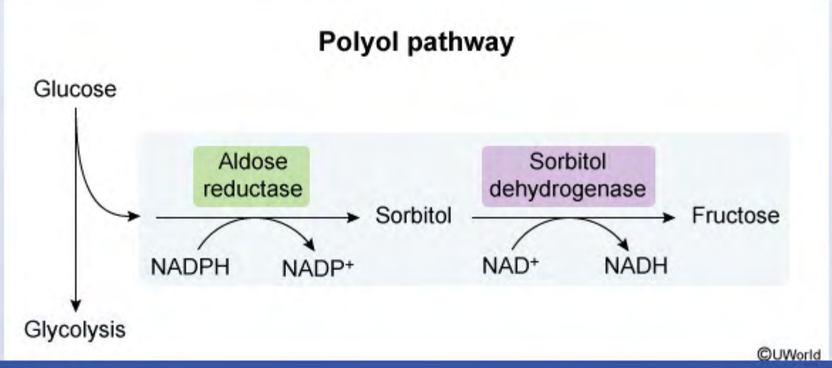
Incorrect
Correct answer
C

83%
Answered correctly

03 secs
Time Spent

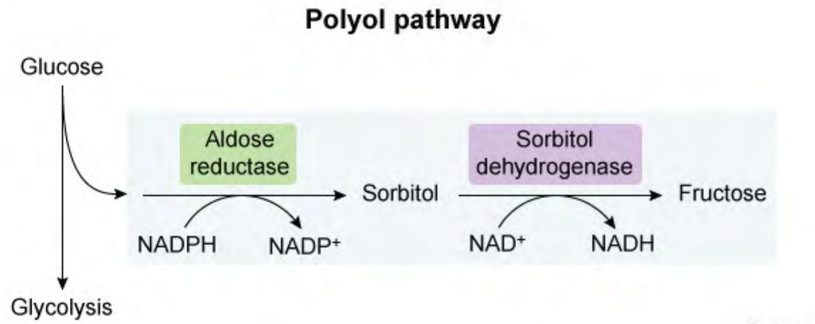
2023
Version

Explanation



https://t.me/USMLEWorldStep1

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

- **Polyol pathway overactivity:** The enzyme aldose reductase converts **glucose to sorbitol**, which is then

https://t.me/USMLEWorldStep1



©UWorld

This patient has **cataracts**, an opacification of the lens of the eye that can lead to blindness, likely a result of long-standing **hyperglycemia** due to poorly controlled diabetes mellitus. Certain cells (eg, retinal, endothelial, lens, renal mesangial, Schwann) are more vulnerable to hyperglycemia-induced damage because they are unable to regulate glucose transport when circulating levels are high.

Multiple metabolic pathways are involved in the pathogenesis of hyperglycemia-induced tissue damage:

- **Advanced glycosylation end-products (AGEs):** Glucose can nonenzymatically attach to proteins and lipids, forming reversible glycosylation products that slowly stabilize into irreversible products. Under hyperglycemic conditions, AGEs accumulate and facilitate deposition of LDL in blood vessel walls and inflammatory cell invasion that causes atherosclerosis and microangiopathic complications. High glucose levels in the aqueous humor may also induce nonenzymatic glycation of lens proteins, which contributes to cataract formation.
- **Polyol pathway overactivity:** The enzyme aldose reductase converts **glucose to sorbitol**, which is then oxidized to fructose by the enzyme sorbitol dehydrogenase. With hyperglycemia, formation of sorbitol occurs faster than its metabolism to fructose, resulting in its accumulation. Sorbitol increases the osmotic pressure in tissues and stimulates the influx of water, leading to **osmotic cellular injury**. In addition, **oxidative stress** resulting from the depletion of NADPH (aldose reductase consumes NADPH) also contributes to cataract formation and other diabetic complications such as retinopathy, peripheral neuropathy, and nephropathy.

(Choices A and B) Aldose reductase also catalyzes the conversion of galactose (obtained from dietary lactose) to galactitol, but sorbitol dehydrogenase is incapable of oxidizing galactitol to its corresponding keto sugar (tagatose, a food sweetener). In galactosemia (galactose 1-phosphate uridyltransferase deficiency), excess galactitol is produced, which causes cataracts in newborns.

(Choice D) In the hexose monophosphate shunt, glucose-6-phosphate is converted to 6-phosphogluconolactone by the enzyme glucose-6-phosphate dehydrogenase (G6PD), generating the reducing equivalent NADPH. G6PD deficiency results in hemolytic anemia during times of increased oxidative stress.

https://t.me/USMLEWorldStep1

hyperglycemic conditions, AGEs accumulate and facilitate deposition of LDL in blood vessel walls and inflammatory cell invasion that causes atherosclerosis and microangiopathic complications. High glucose levels in the aqueous humor may also induce nonenzymatic glycation of lens proteins, which contributes to cataract formation.

- **Polyol pathway overactivity:** The enzyme aldose reductase converts **glucose to sorbitol**, which is then oxidized to fructose by the enzyme sorbitol dehydrogenase. With hyperglycemia, formation of sorbitol occurs faster than its metabolism to fructose, resulting in its accumulation. Sorbitol increases the osmotic pressure in tissues and stimulates the influx of water, leading to **osmotic cellular injury**. In addition, **oxidative stress** resulting from the depletion of NADPH (aldose reductase consumes NADPH) also contributes to cataract formation and other diabetic complications such as retinopathy, peripheral neuropathy, and nephropathy.

(Choices A and B) Aldose reductase also catalyzes the conversion of galactose (obtained from dietary lactose) to galactitol, but sorbitol dehydrogenase is incapable of oxidizing galactitol to its corresponding keto sugar (tagatose, a food sweetener). In galactosemia (galactose 1-phosphate uridyltransferase deficiency), excess galactitol is produced, which causes cataracts in newborns.

(Choice D) In the hexose monophosphate shunt, glucose-6-phosphate is converted to 6-phosphogluconolactone by the enzyme glucose-6-phosphate dehydrogenase (G6PD), generating the reducing equivalent NADPH. G6PD deficiency results in hemolytic anemia during times of increased oxidative stress.

(Choice E) Lactate dehydrogenase catalyzes the conversion of pyruvate to lactate under anaerobic conditions. Excess lactate forms in hypoxic states, causing metabolic acidosis.

Educational objective:
In hyperglycemic states, aldose reductase converts glucose to sorbitol at a rate faster than sorbitol can be metabolized. Sorbitol accumulates in certain cells such as lens cells, causing an influx of water and resulting in osmotic cellular injury. Depletion of NADPH by aldose reductase also increases oxidative stress, which accelerates development of cataracts and diabetic microvascular complications (eg, neuropathy, retinopathy).

References

- The pathobiology of diabetic complications: a unifying mechanism.

https://t.me/USMLEWorldStep1

Researchers studying the pathophysiology of diabetes mellitus identify a family with an inherited mutation in the insulin gene. The mutation results in a single amino acid substitution in the proinsulin molecule. However, affected family members are asymptomatic, and most have completely normal blood glucose levels. Analysis of the mature insulin molecule shows that it is identical to normal human insulin. The researchers conclude that the amino acid substitution affects a segment of proinsulin removed during post-translational processing of the protein. The polypeptide segment containing the mutation is most likely to undergo which of the following processes within pancreatic beta cells?

- A. Degradation in lysosomes
- B. Degradation in proteasomes
- C. Degradation in the rough endoplasmic reticulum
- D. Direct translocation across the plasma membrane
- E. Storage in secretory granules

Submit

https://t.me/USMLEWorldStep1

Researchers studying the pathophysiology of diabetes mellitus identify a family with an inherited mutation in the insulin gene. The mutation results in a single amino acid substitution in the proinsulin molecule. However, affected family members are asymptomatic, and most have completely normal blood glucose levels. Analysis of the mature insulin molecule shows that it is identical to normal human insulin. The researchers conclude that the amino acid substitution affects a segment of proinsulin removed during post-translational processing of the protein. The polypeptide segment containing the mutation is most likely to undergo which of the following processes within pancreatic beta cells?

- ✗ A. Degradation in lysosomes (9%)
- B. Degradation in proteasomes (30%)
- C. Degradation in the rough endoplasmic reticulum (8%)
- D. Direct translocation across the plasma membrane (13%)
- ✓ E. Storage in secretory granules (39%)

Incorrect
Correct answer
E

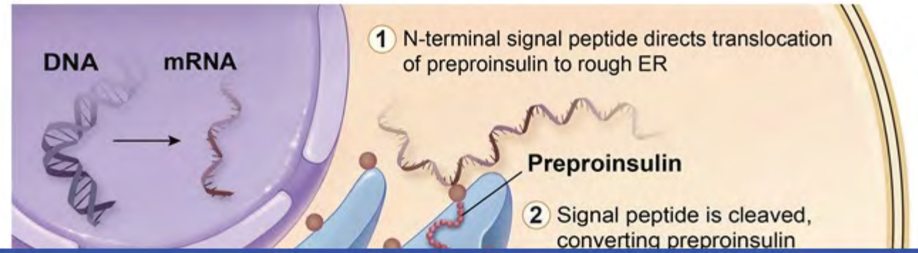
39%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

Insulin synthesis and secretion



https://t.me/USMLEWorldStep1

Correct answer
E

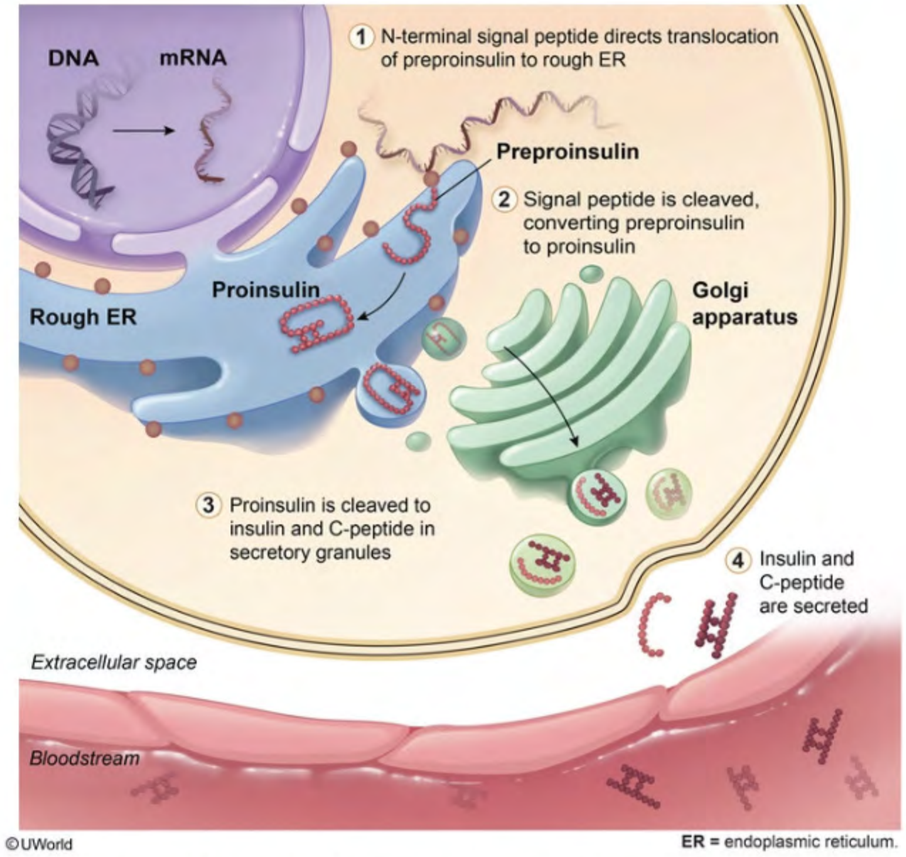
Answered correctly

Time Spent

Version

Exhibit Display

Insulin synthesis and secretion



©UWorld

ER = endoplasmic reticulum.

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

©UWorld
ER = endoplasmic reticulum.

Insulin, a polypeptide hormone synthesized by pancreatic beta cells, is released in response to elevated glucose

https://t.me/USMLEWorldStep1

©UWorld

ER = endoplasmic reticulum.

Insulin, a polypeptide hormone synthesized by pancreatic beta cells, is released in response to elevated glucose levels. Insulin mRNA codes for **preproinsulin**, a larger precursor molecule that begins with a hydrophobic N-terminal signal peptide. Shortly after translation begins, this signal sequence interacts with cytosolic signal recognition peptide, which halts protein synthesis until the ribosome translocates to the rough endoplasmic reticulum (RER). Once bound to the RER, translation resumes and the growing peptide chain is extruded into the RER. The N-terminal signal peptide is then cleaved from preproinsulin to yield **proinsulin**.

Proinsulin undergoes conformational changes and the addition of 3 disulfide bonds in the RER. Proinsulin is then transported to the Golgi apparatus, where it is packed into secretory granules. Endopeptidases in the secretory granules cleave proinsulin into **insulin** and **C-peptide**, which are then stored within the granules until they are secreted from the cell via exocytosis **(Choices A, B, and C)**.

Exogenous insulin administered to patients with diabetes does not contain C-peptide. However, C-peptide released from beta cells remains in the circulation with a half-life of approximately 35 minutes and can be assayed as a surrogate marker for endogenous insulin production.

(Choice D) Most proteins destined for the extracellular space have a signaling sequence that directs them to the RER/Golgi apparatus, where they are packaged into secretory vesicles. However, a few proteins, such as interleukin-1, lack a signaling sequence and are secreted directly from the cytoplasm via an unconventional mechanism.

Educational objective:
Cleavage of proinsulin in pancreatic beta-cell secretory granules yields insulin and C-peptide, which are stored in the granules until they are secreted in equimolar amounts.

References

- Regulation of insulin synthesis and secretion and pancreatic beta-cell dysfunction in diabetes.

Physiology	Endocrine, Diabetes & Metabolism	Diabetes mellitus
Subject	System	Topic

Copyright © UWorld. All rights reserved.

https://t.me/USMLEWorldStep1

©UWorld

ER = endoplasmic reticulum.

Insulin
levels.
termin
recogn
reticul
RER.

Proins
transp
granul
secret

Exoge
releas
as a s

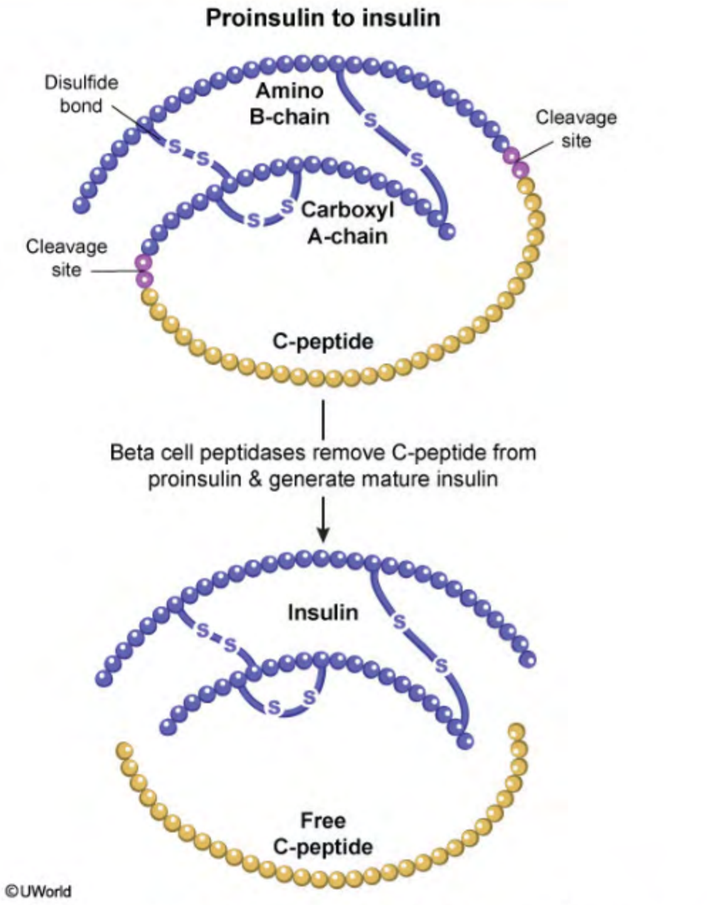
(Choi
RER/C
interle
mecha

Educa
Cleava
the gra

Refere
- Reg

Physiolo
Subject System Topic

Exhibit Display



Zoom In Zoom Out Reset New | Existing My Notebook

Copyright © UWorld. All rights reserved.

https://t.me/USMLEWorldStep1

A 22-year-old man comes to the office for evaluation of a neck mass. He first noticed a small nodule in his lower neck 6 months ago, and it has progressively enlarged since that time. The patient has had no changes in weight and otherwise feels well. Medical history is notable only for seasonal allergies, and he takes no medications. Physical examination shows a 2-cm nodule in the right lobe of the thyroid. There are multiple 4- to 8-mm soft papules on the lips and tongue. The arm span exceeds his height and the patient has long fingers. Serum calcitonin levels are elevated. Which of the following is most likely to develop in this patient?

- A. Episodic headache
- B. Hypercalcemia
- C. Hypoglycemic episodes
- D. Peripheral vision loss
- E. Recurrent peptic ulcers

Submit

https://t.me/USMLEWorldStep1

A 22-year-old man comes to the office for evaluation of a neck mass. He first noticed a small nodule in his lower neck 6 months ago, and it has progressively enlarged since that time. The patient has had no changes in weight and otherwise feels well. Medical history is notable only for seasonal allergies, and he takes no medications. Physical examination shows a 2-cm nodule in the right lobe of the thyroid. There are multiple 4- to 8-mm soft papules on the lips and tongue. The arm span exceeds his height and the patient has long fingers. Serum calcitonin levels are elevated. Which of the following is most likely to develop in this patient?

- ✓ A. Episodic headache (65%)
- ✗ B. Hypercalcemia (14%)
- C. Hypoglycemic episodes (5%)
- D. Peripheral vision loss (8%)
- E. Recurrent peptic ulcers (5%)

Incorrect
Correct answer
A

65%
Answered correctly

04 secs
Time Spent

2023
Version

Explanation

Classification of multiple endocrine neoplasia	
Type 1	• **Primary hyperparathyroidism** (parathyroid adenomas or hyperplasia) • Pituitary tumors (prolactin, visual defects) • Pancreatic tumors (especially gastrinomas)
Type	• **Medullary thyroid cancer** (calcitonin) • Pheochromocytoma

https://t.me/USMLEWorldStep1

Classification of multiple endocrine neoplasia	
Type 1	• **Primary hyperparathyroidism** (parathyroid adenomas or hyperplasia) • Pituitary tumors (prolactin, visual defects) • Pancreatic tumors (especially gastrinomas)
Type 2A	• **Medullary thyroid cancer** (calcitonin) • Pheochromocytoma • Primary hyperparathyroidism (parathyroid hyperplasia)
Type 2B	• **Medullary thyroid cancer** (calcitonin) • Pheochromocytoma • Mucosal neuromas/marfanoid habitus

This patient has an enlarging thyroid nodule associated with an elevated calcitonin level, which is concerning for **medullary thyroid cancer** (MTC), a malignancy arising from the thyroid C (parafollicular) cells. These findings, in association with mucosal neuromas and **marfanoid habitus** (eg, arm span > height, long fingers, joint laxity), suggest **multiple endocrine neoplasia type 2B** (MEN2B). MEN2 syndromes are caused by germline mutations of the ***RET*** proto-oncogene. MTC is present in nearly all patients with MEN2 and is usually more aggressive and occurs at an earlier age than sporadic MTC.

Pheochromocytomas develop in roughly half of patients with MEN2 syndromes and cause paroxysmal hypertension and tachycardia due to the intermittent secretion of catecholamines. The abrupt, severe increase in blood pressure can precipitate **episodic headaches** and is often accompanied by other symptoms associated with catecholamine excess (eg, diaphoresis, tremor, chest pain).

(Choice B) Hyperparathyroidism with secondary hypercalcemia is the most common manifestation of MEN1. Hyperparathyroidism (due to parathyroid chief cell hyperplasia or adenoma formation) is also seen in 10%-20% of patients with MEN2A, but it is not a feature of MEN2B.

(Choices C and E) Many patients with MEN1 have endocrine pancreatic tumors that secrete gastrin, leading to

https://t.me/USMLEWorldStep1

Type 2B	• **Medullary thyroid cancer** (calcitonin) • Pheochromocytoma • Mucosal neuromas/marfanoid habitus

This patient has an enlarging thyroid nodule associated with an elevated calcitonin level, which is concerning for **medullary thyroid cancer** (MTC), a malignancy arising from the thyroid C (parafollicular) cells. These findings, in association with mucosal neuromas and **marfanoid habitus** (eg, arm span > height, long fingers, joint laxity), suggest **multiple endocrine neoplasia type 2B** (MEN2B). MEN2 syndromes are caused by germline mutations of the ***RET*** proto-oncogene. MTC is present in nearly all patients with MEN2 and is usually more aggressive and occurs at an earlier age than sporadic MTC.

Pheochromocytomas develop in roughly half of patients with MEN2 syndromes and cause paroxysmal hypertension and tachycardia due to the intermittent secretion of catecholamines. The abrupt, severe increase in blood pressure can precipitate **episodic headaches** and is often accompanied by other symptoms associated with catecholamine excess (eg, diaphoresis, tremor, chest pain).

(Choice B) Hyperparathyroidism with secondary hypercalcemia is the most common manifestation of MEN1. Hyperparathyroidism (due to parathyroid chief cell hyperplasia or adenoma formation) is also seen in 10%-20% of patients with MEN2A, but it is not a feature of MEN2B.

(Choices C and E) Many patients with MEN1 have endocrine pancreatic tumors that secrete gastrin, leading to refractory peptic ulceration and diarrhea (Zollinger-Ellison syndrome). In rare cases, endocrine tumors of the pancreas in MEN1 secrete other hormones, such as insulin, which can cause hypoglycemia.

(Choice D) Pituitary tumors are present in 50% of patients with MEN1. Large pituitary tumors with suprasellar extensions are likely to cause peripheral vision loss.

Educational objective:
Multiple endocrine neoplasia type 2B is characterized by medullary thyroid cancer, pheochromocytomas, mucosal neuromas, and marfanoid habitus. Hyperparathyroidism is not a feature of this syndrome.

References

https://t.me/USMLEWorldStep1

- **Medullary thyroid cancer** (calcitonin)

Exhibit Display

Mucosal neuromas



*Associated with multiple endocrine neoplasia type 2B (MEN 2B).

©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

This p
medul
associ
sugge
of the
occurs

Pheoc
hypert
blood
catech

(Choi
Hyperp
patien

(Choi
refract
pancre

(Choi
extens

Educa
Multipl
neuror

References

https://t.me/USMLEWorldStep1

A 24-year-old man diagnosed with diabetes mellitus 2 years ago is brought to the emergency department after a temporary loss of consciousness. He was getting ready to eat and administered a preprandial insulin injection, but he was distracted by a phone call from work and ended up skipping the meal. His girlfriend found him passed out in his bedroom and administered glucagon immediately. The patient recovered consciousness within 15 minutes. Metabolic changes in which of the following organs are most likely responsible for this patient's recovery?

- A. Adipose tissue
- B. Adrenals
- C. Kidney
- D. Liver
- E. Pancreas
- F. Skeletal muscles
- G. Small intestine

Submit

https://t.me/USMLEWorldStep1

A 24-year-old man diagnosed with diabetes mellitus 2 years ago is brought to the emergency department after a temporary loss of consciousness. He was getting ready to eat and administered a preprandial insulin injection, but he was distracted by a phone call from work and ended up skipping the meal. His girlfriend found him passed out in his bedroom and administered glucagon immediately. The patient recovered consciousness within 15 minutes. Metabolic changes in which of the following organs are most likely responsible for this patient's recovery?

- A. Adipose tissue (2%)
- ✗ B. Adrenals (1%)
- C. Kidney (0%)
- ✓ D. Liver (86%)
- E. Pancreas (3%)
- F. Skeletal muscles (4%)
- G. Small intestine (0%)

Incorrect
Correct answer
D

86%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

Glucagon increases serum glucose by increasing hepatic glucose production via **glycogenolysis** (breakdown of glycogen) and **gluconeogenesis** (production of glucose from noncarbohydrate sources). Glucagon-induced glycogenolysis is the predominant initial means of rapidly increasing blood glucose levels during hypoglycemia.

Glucagon functions by stimulating G protein–coupled receptors on hepatocytes, increasing intracellular cAMP concentration and activating protein kinase A. This leads to activation of the key glycogenolytic enzyme, glycogen phosphorylase. It also stimulates gluconeogenesis by activating rate-limiting gluconeogenetic enzymes (eg, pyruvate carboxylase, phosphoenolpyruvate carboxykinase) and decreasing intracellular fructose 2,6

https://t.me/USMLEWorldStep1

Explanation

Glucagon increases serum glucose by increasing hepatic glucose production via **glycogenolysis** (breakdown of glycogen) and **gluconeogenesis** (production of glucose from noncarbohydrate sources). Glucagon-induced glycogenolysis is the predominant initial means of rapidly increasing blood glucose levels during hypoglycemia.

Glucagon functions by stimulating G protein–coupled receptors on hepatocytes, increasing intracellular cAMP concentration and activating protein kinase A. This leads to activation of the key glycogenolytic enzyme, glycogen phosphorylase. It also stimulates gluconeogenesis by activating rate-limiting gluconeogenetic enzymes (eg, pyruvate carboxylase, phosphoenolpyruvate carboxykinase) and decreasing intracellular fructose-2,6-bisphosphate levels (inhibiting glycolysis).

(Choices A, B, and F) Epinephrine from the adrenals increases glucose by multiple mechanisms, including increased glycogenolysis and gluconeogenesis in the liver and decreased glucose uptake by skeletal muscle. Epinephrine also causes increased alanine release from skeletal muscle, which serves as a source of gluconeogenesis in the liver. In adipose tissue, epinephrine increases the breakdown of triglycerides, thereby increasing circulating free fatty acids and glycerol that can be utilized as gluconeogenetic substrates.

(Choice C) During the first 12 hours of fasting, hepatic glycogenolysis is the source for most of the body's glucose. When hypoglycemia is sustained, gluconeogenesis in the renal cortex becomes an important glucose source. Epinephrine is more effective than glucagon in stimulating renal gluconeogenesis.

(Choice E) Glucagon and insulin are pancreatic hormones that act as key blood glucose regulators. Insulin decreases blood glucose levels and suppresses glucagon secretion. Although it sounds counterintuitive, glucagon stimulates insulin secretion by acting on the pancreatic beta cells (allowing glucose to be taken up by insulin-sensitive tissues).

(Choice G) The treatment of choice in hypoglycemic patients without an altered sensorium is to administer glucose orally as glucose is a monosaccharide that gets absorbed rapidly from the gastrointestinal tract.

Educational objective:
Glucagon increases serum glucose by increasing hepatic glycogenolysis and gluconeogenesis. Glucagon also stimulates insulin secretion from the pancreas. Unlike epinephrine, glucagon has an insignificant effect on glucose

https://t.me/USMLEWorldStep1

glycogenolysis is the predominant initial means of rapidly increasing blood glucose levels during hypoglycemia.

Glucagon functions by stimulating G protein–coupled receptors on hepatocytes, increasing intracellular cAMP concentration and activating protein kinase A. This leads to activation of the key glycogenolytic enzyme, glycogen phosphorylase. It also stimulates gluconeogenesis by activating rate-limiting gluconeogenetic enzymes (eg, pyruvate carboxylase, phosphoenolpyruvate carboxykinase) and decreasing intracellular fructose-2,6-bisphosphate levels (inhibiting glycolysis).

(Choices A, B, and F) Epinephrine from the adrenals increases glucose by multiple mechanisms, including increased glycogenolysis and gluconeogenesis in the liver and decreased glucose uptake by skeletal muscle. Epinephrine also causes increased alanine release from skeletal muscle, which serves as a source of gluconeogenesis in the liver. In adipose tissue, epinephrine increases the breakdown of triglycerides, thereby increasing circulating free fatty acids and glycerol that can be utilized as gluconeogenetic substrates.

(Choice C) During the first 12 hours of fasting, hepatic glycogenolysis is the source for most of the body's glucose. When hypoglycemia is sustained, gluconeogenesis in the renal cortex becomes an important glucose source. Epinephrine is more effective than glucagon in stimulating renal gluconeogenesis.

(Choice E) Glucagon and insulin are pancreatic hormones that act as key blood glucose regulators. Insulin decreases blood glucose levels and suppresses glucagon secretion. Although it sounds counterintuitive, glucagon stimulates insulin secretion by acting on the pancreatic beta cells (allowing glucose to be taken up by insulin-sensitive tissues).

(Choice G) The treatment of choice in hypoglycemic patients without an altered sensorium is to administer glucose orally as glucose is a monosaccharide that gets absorbed rapidly from the gastrointestinal tract.

Educational objective:
Glucagon increases serum glucose by increasing hepatic glycogenolysis and gluconeogenesis. Glucagon also stimulates insulin secretion from the pancreas. Unlike epinephrine, glucagon has an insignificant effect on glucose homeostasis in the skeletal muscle, adipose tissue, and renal cortex.

References

- Physiologic action of glucagon on liver glucose metabolism.

https://t.me/USMLEWorldStep1

A 28-year-old woman comes to the office due to a 4-month history of amenorrhea. She has also had a whitish nipple discharge from both breasts. The patient has taken several pregnancy tests at home that have been negative. She has also had increased fatigue, depressed mood, and weight gain over this time. The patient has had no headaches or vision changes. She has no prior medical problems and takes no medications. On physical examination, there is thinning of the outer third of the eyebrows. The thyroid is enlarged and nontender to palpation. Abdominal and pelvic examinations are normal. The skin appears dry. Laboratory results are as follows:

Beta-hCG, serum	negative
Thyroxine (T4)	2.5 µg/dL
TSH	11.0 µU/mL
Prolactin	30 ng/mL (<20 ng/mL)
Antithyroid peroxidase antibodies	positive

Which of the following is the most likely mechanism causing this patient's elevated prolactin level?

- A. Activation of lactotrophs by antithyroid peroxidase antibodies
- B. Binding of dopamine receptors by antithyroid peroxidase antibodies
- C. Inhibition of dopamine release by TSH
- D. Stimulation of lactotrophs by thyrotropin-releasing hormone (TRH)
- E. TRH-induced overproduction of dopamine
- F. TSH-mediated activation of lactotrophs

Submit

https://t.me/USMLEWorldStep1

A 28-year-old woman comes to the office due to a 4-month history of amenorrhea. She has also had a whitish nipple discharge from both breasts. The patient has taken several pregnancy tests at home that have been negative. She has also had increased fatigue, depressed mood, and weight gain over this time. The patient has had no headaches or vision changes. She has no prior medical problems and takes no medications. On physical examination, there is thinning of the outer third of the eyebrows. The thyroid is enlarged and nontender to palpation. Abdominal and pelvic examinations are normal. The skin appears dry. Laboratory results are as follows:

Beta-hCG, serum	negative
Thyroxine (T4)	2.5 µg/dL
TSH	11.0 µU/mL
Prolactin	30 ng/mL (<20 ng/mL)
Antithyroid peroxidase antibodies	positive

Which of the following is the most likely mechanism causing this patient's elevated prolactin level?

- A. Activation of lactotrophs by antithyroid peroxidase antibodies (2%)
- ✗ B. Binding of dopamine receptors by antithyroid peroxidase antibodies (5%)
- C. Inhibition of dopamine release by TSH (22%)
- ✓ D. Stimulation of lactotrophs by thyrotropin-releasing hormone (TRH) (53%)
- E. TRH-induced overproduction of dopamine (2%)
- F. TSH-mediated activation of lactotrophs (13%)

Incorrect
Correct answer
D

53%
Answered correctly

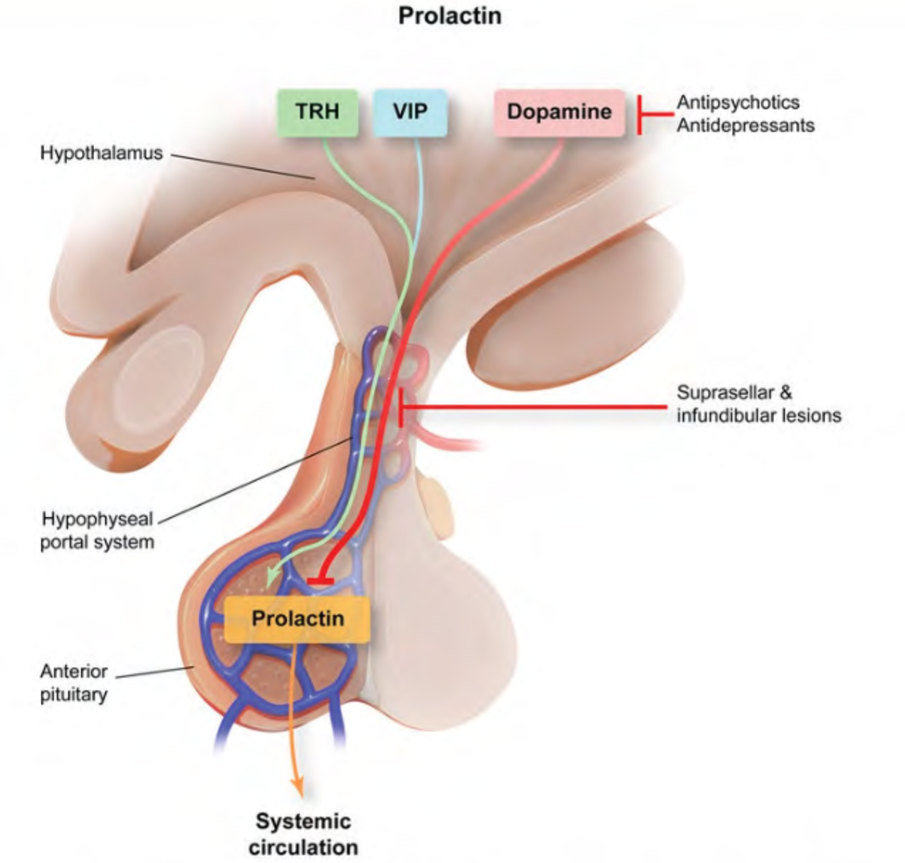
03 secs
Time Spent

2023
Version

https://t.me/USMLEWorldStep1

F. TSH-mediated activation of lactotrophs (13%)

Exhibit Display



Zoom In Zoom Out Reset New | Existing My Notebook

https://t.me/USMLEWorldStep1

This patient has symptoms of hypothyroidism (eg, fatigue, weight gain, goiter, thinning of outer eyebrow edges). Her low thyroxine (T4), elevated TSH, and antithyroid peroxidase antibodies are further indicative of **primary hypothyroidism** from chronic autoimmune (Hashimoto) thyroiditis. In patients with primary hypothyroidism, there is a compensatory increase in hypothalamic thyrotropin-releasing hormone (TRH) production as thyroid hormone levels fall, stimulating increased secretion of TSH by the pituitary.

Prolactin is regulated primarily by the inhibitory effects of dopaminergic neurons from the hypothalamus. However, lactotroph cells express TRH receptors, and TRH stimulates synthesis and release of prolactin. The **elevated TRH levels** in the pituitary in patients with primary hypothyroidism can therefore **increase prolactin secretion** and lead to hyperprolactinemia.

In premenopausal women, hyperprolactinemia can cause **galactorrhea**. Prolactin suppresses GnRH secretion from the hypothalamus, leading to reduced secretion of LH (and to a lesser extent FSH) and subsequent hypogonadism, anovulation, and **amenorrhea**. Symptoms in men are often nonspecific, but can include infertility, decreased libido, and impotence.

(Choices A and B) The most common cause of primary hypothyroidism is chronic autoimmune (Hashimoto) thyroiditis. Most patients with Hashimoto thyroiditis produce thyroid peroxidase autoantibodies, but it is TRH (not the autoantibodies) that triggers prolactin release.

(Choice C) Antidopaminergic drugs (eg, antipsychotics, metoclopramide) can reduce the inhibitory effect of dopamine on prolactin secretion and lead to hyperprolactinemia, but TSH has little effect on dopamine pathways.

(Choice E) The stimulatory effect of TRH on pituitary lactotrophs is mediated by TRH receptors on lactotroph cells, not by effects on dopaminergic pathways. Overproduction of dopamine would inhibit lactotroph activity.

(Choice F) Effects of the hypothalamic-pituitary-thyroid axis on prolactin secretion are mediated primarily by TRH, not TSH.

Educational objective:
Prolactin production is regulated primarily by inhibitory effects of hypothalamic dopaminergic pathways. However, prolactin secretion is stimulated by thyrotropin-releasing hormone (TRH). In patients with primary hypothyroidism, the increased production of TRH by the hypothalamus can lead to hyperprolactinemia.

https://t.me/USMLEWorldStep1

A 55-year-old woman comes to the office due to increasing fatigability and a 4.54-kg (10-lb) weight gain over the last few months. The patient used to swim daily but now does so only once or twice a week due to fatigue. She takes a daily multivitamin and an over-the-counter medication for constipation. Blood pressure is 140/96 mm Hg and pulse is 55/min. Physical examination shows hair loss involving the lateral third of the eyebrows. There is delayed relaxation of the deep tendon reflexes of the knee and ankle. Which of the following laboratory tests is the most appropriate next step in evaluation of this patient's symptoms?

- A. 24-hour urinary cortisol excretion test
- B. Dexamethasone suppression test
- C. Fasting plasma glucose level
- D. Serum iron studies
- E. Serum triiodothyronine and thyroxine levels
- F. Serum TSH level

Submit

https://t.me/USMLEWorldStep1

A 55-year-old woman comes to the office due to increasing fatigability and a 4.54-kg (10-lb) weight gain over the last few months. The patient used to swim daily but now does so only once or twice a week due to fatigue. She takes a daily multivitamin and an over-the-counter medication for constipation. Blood pressure is 140/96 mm Hg and pulse is 55/min. Physical examination shows hair loss involving the lateral third of the eyebrows. There is delayed relaxation of the deep tendon reflexes of the knee and ankle. Which of the following laboratory tests is the most appropriate next step in evaluation of this patient's symptoms?

- A. 24-hour urinary cortisol excretion test (3%)
- ✗ B. Dexamethasone suppression test (2%)
- C. Fasting plasma glucose level (0%)
- D. Serum iron studies (0%)
- E. Serum triiodothyronine and thyroxine levels (16%)
- ✓ F. Serum TSH level (75%)

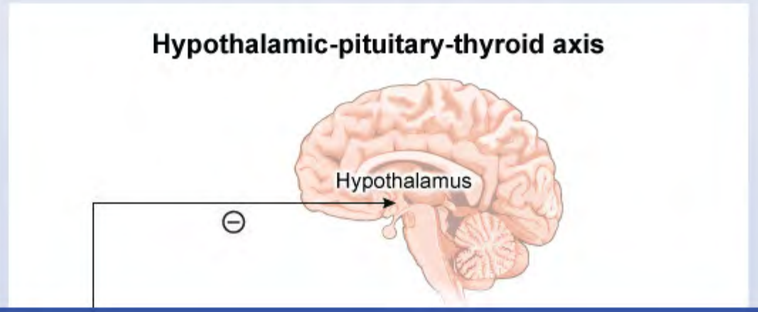
Incorrect
Correct answer
F

75%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation



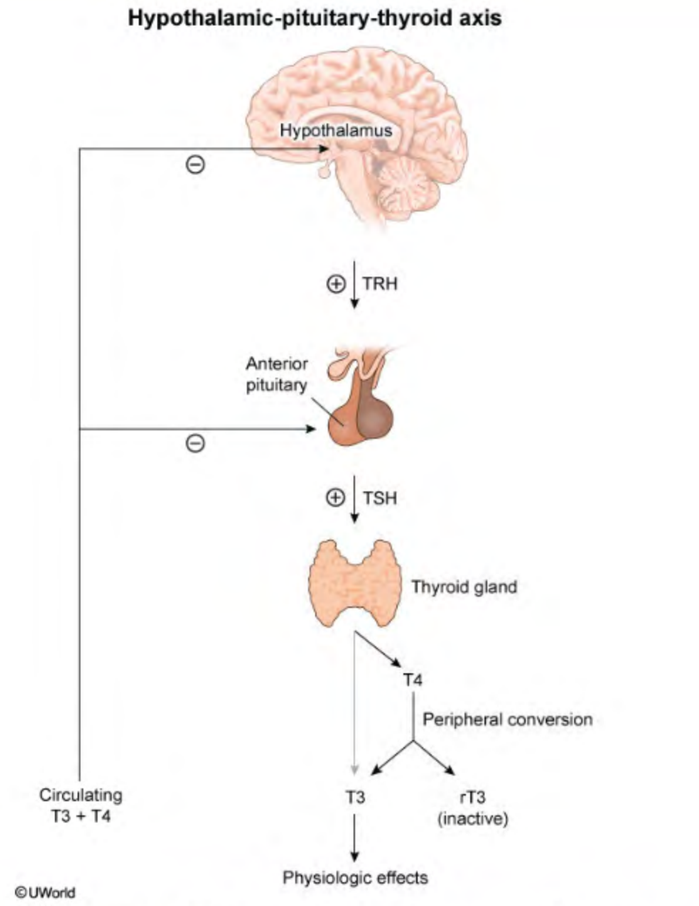
https://t.me/USMLEWorldStep1

A 55-year-old woman comes to the office due to increasing fatigability and a 4.54-kg (10-lb) weight gain over the last fe
takes
and pu
delaye
most a

Incc
Corre
F

Expl

Exhibit Display



Zoom In Zoom Out Reset New | Existing My Notebook

https://t.me/USMLEWorldStep1

©UWorld

Physiologic effects

This patient's symptoms (eg, fatigue, weight gain, constipation) and examination findings suggest **hypothyroidism**. Vital signs typically show bradycardia and hypertension (due to increased vascular resistance). Hypothyroidism can also cause slowed hair growth and alterations in hair growth cycles, leading to thinning of the scalp hair and lateral eyebrows. Slowed reuptake of calcium by the sarcoplasmic reticulum manifests as a delayed relaxation phase of deep tendon reflexes.

Most patients with hypothyroidism have **primary hypothyroidism** (ie, dysfunction within the thyroid gland). The thyroid releases thyroid hormones (triiodothyronine [T3] and thyroxine [T4]) in response to TSH from the pituitary. In turn, TSH secretion is regulated by thyrotropin-releasing hormone (TRH) from the hypothalamus. Thyroid hormone suppresses TSH and TRH via negative feedback, and **small changes in thyroid hormone** levels lead to **large changes in TSH** levels. As thyroid hormone production slows, TSH secretion increases rapidly to restore thyroid activity, often before T4 levels fall below standard laboratory reference ranges. Therefore, **serum TSH** is the **most sensitive** marker for primary hypothyroidism.

(Choices A and B) The 24-hour urinary cortisol assay and the dexamethasone suppression test are used to screen for Cushing syndrome. Although this patient is hypertensive, she does not have other Cushingoid features (eg, central obesity, skin striae, proximal muscle weakness).

(Choice C) Initial tests for diabetes mellitus include fasting glucose, hemoglobin A1c, and oral glucose tolerance tests. Diabetes can cause peripheral neuropathy (eg, paresthesias, loss of distal sensation, decreased ankle reflexes), but bradycardia, diastolic hypertension, and delayed relaxation of reflexes are more suggestive of hypothyroidism.

(Choice D) The initial evaluation of hereditary hemochromatosis includes serum iron studies (eg, serum iron, ferritin, transferrin saturation). Although pituitary dysfunction with secondary (central) hypothyroidism can occur, patients commonly also have arthritis, diabetes mellitus, abnormal skin pigmentation, and hepatomegaly.

(Choice E) TSH is more sensitive than either T3 or T4 for diagnosing primary hypothyroidism. TSH is not elevated in pituitary or hypothalamic disease (ie, secondary hypothyroidism), but this is a much less common cause of hypothyroidism (<5% of cases). In addition, patients with secondary hypothyroidism usually have other clinical features of hypothalamic or pituitary dysfunction.

https://t.me/USMLEWorldStep1

Most patients with hypothyroidism have **primary hypothyroidism** (ie, dysfunction within the thyroid gland). The thyroid releases thyroid hormones (triiodothyronine [T3] and thyroxine [T4]) in response to TSH from the pituitary. In turn, TSH secretion is regulated by thyrotropin-releasing hormone (TRH) from the hypothalamus. Thyroid hormone suppresses TSH and TRH via negative feedback, and **small changes in thyroid hormone** levels lead to **large changes in TSH** levels. As thyroid hormone production slows, TSH secretion increases rapidly to restore thyroid activity, often before T4 levels fall below standard laboratory reference ranges. Therefore, **serum TSH** is the **most sensitive** marker for primary hypothyroidism.

(Choices A and B) The 24-hour urinary cortisol assay and the dexamethasone suppression test are used to screen for Cushing syndrome. Although this patient is hypertensive, she does not have other Cushingoid features (eg, central obesity, skin striae, proximal muscle weakness).

(Choice C) Initial tests for diabetes mellitus include fasting glucose, hemoglobin A1c, and oral glucose tolerance tests. Diabetes can cause peripheral neuropathy (eg, paresthesias, loss of distal sensation, decreased ankle reflexes), but bradycardia, diastolic hypertension, and delayed relaxation of reflexes are more suggestive of hypothyroidism.

(Choice D) The initial evaluation of hereditary hemochromatosis includes serum iron studies (eg, serum iron, ferritin, transferrin saturation). Although pituitary dysfunction with secondary (central) hypothyroidism can occur, patients commonly also have arthritis, diabetes mellitus, abnormal skin pigmentation, and hepatomegaly.

(Choice E) TSH is more sensitive than either T3 or T4 for diagnosing primary hypothyroidism. TSH is not elevated in pituitary or hypothalamic disease (ie, secondary hypothyroidism), but this is a much less common cause of hypothyroidism (<5% of cases). In addition, patients with secondary hypothyroidism usually have other clinical features of hypothalamic or pituitary dysfunction.

Educational objective:
The thyroid releases thyroid hormone (triiodothyronine [T3] and thyroxine [T4]) in response to TSH from the pituitary, which is regulated by thyrotropin-releasing hormone (TRH) from the hypothalamus. Thyroid hormone suppresses the secretion of TSH and TRH via negative feedback, and small changes in thyroid hormone levels cause large changes in TSH. Serum TSH is the most sensitive test for primary hypothyroidism.

References

https://t.me/USMLEWorldStep1

A 51-year-old woman comes to the office due to progressively worsening fatigue, weight gain, and constipation for the past 6 months. The patient has had difficulty performing daily activities due to her fatigue. She has no significant medical history and takes no medications. The patient has no drug allergies and does not use tobacco, alcohol, or illicit drugs. Blood pressure is 110/80 mm Hg and pulse is 55/min. Physical examination shows mild, diffuse enlargement of the thyroid gland. Cardiopulmonary and abdominal examinations are normal. Biopsy of this patient's thyroid is most likely to show which of the following findings?

- A. Branching papillae with cells containing empty-appearing nuclei
- B. Dense fibrous tissue extending beyond the thyroid capsule
- C. Follicular hyperplasia with tall cells projecting into the follicular lumen
- D. Intense lymphoplasmacytic infiltrate with active germinal centers
- E. Widespread inflammatory infiltrates, giant cells, and disrupted follicles

Submit

https://t.me/USMLEWorldStep1

A 51-year-old woman comes to the office due to progressively worsening fatigue, weight gain, and constipation for the past 6 months. The patient has had difficulty performing daily activities due to her fatigue. She has no significant medical history and takes no medications. The patient has no drug allergies and does not use tobacco, alcohol, or illicit drugs. Blood pressure is 110/80 mm Hg and pulse is 55/min. Physical examination shows mild, diffuse enlargement of the thyroid gland. Cardiopulmonary and abdominal examinations are normal. Biopsy of this patient's thyroid is most likely to show which of the following findings?

- A. Branching papillae with cells containing empty-appearing nuclei (5%)
- ✗ B. Dense fibrous tissue extending beyond the thyroid capsule (5%)
- C. Follicular hyperplasia with tall cells projecting into the follicular lumen (8%)
- ✓ D. Intense lymphoplasmacytic infiltrate with active germinal centers (59%)
- E. Widespread inflammatory infiltrates, giant cells, and disrupted follicles (20%)

Incorrect
Correct answer
D

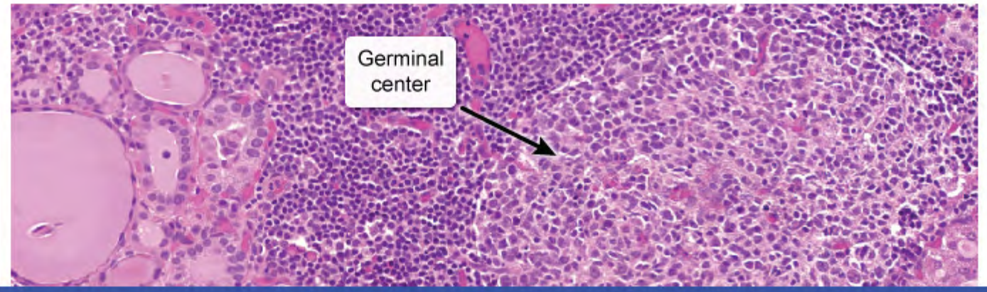
59%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

Hashimoto thyroiditis

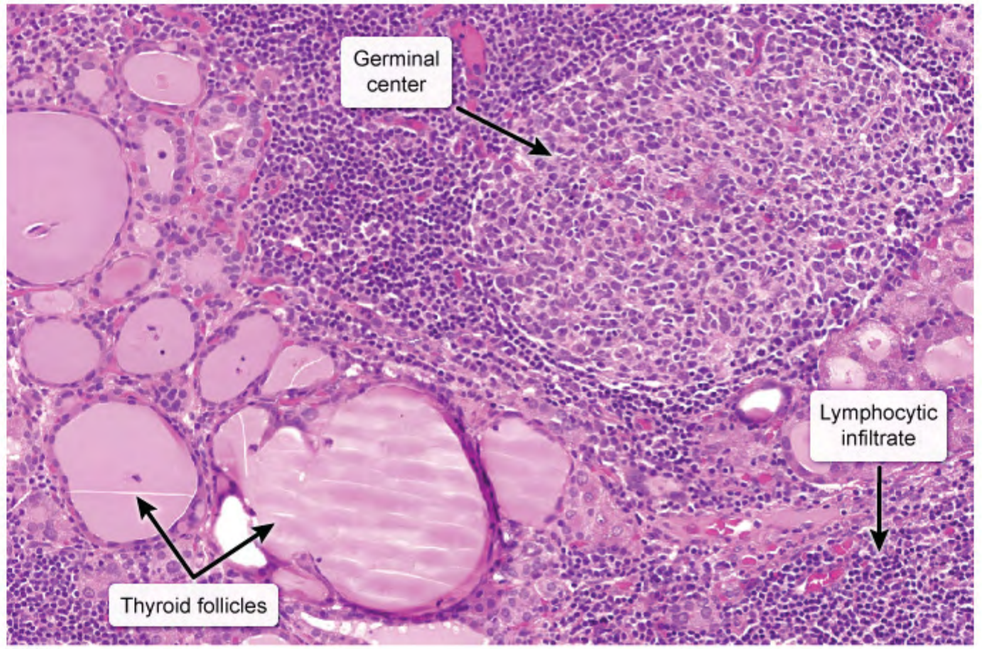


https://t.me/USMLEWorldStep1

A 51-year-old woman comes to the office due to progressively worsening fatigue, weight gain, and constipation for
the pa
signifi
alcoho
diffuse
patien

Exhibit Display

Hashimoto thyroiditis



©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Incc
Corre
D

Expl

https://t.me/USMLEWorldStep1

This patient has **chronic lymphocytic (Hashimoto) thyroiditis** presenting with **hypothyroidism** (eg, fatigue, weight gain, constipation) and a **diffuse goiter**. This autoimmune disease occurs predominately in women, has a peak incidence at age 45-65, and is the most common cause of hypothyroidism in iodine-sufficient regions such as the United States.

In all forms of primary hypothyroidism, laboratory studies show low serum thyroxine (T4) levels and elevated TSH. **Antithyroid peroxidase antibody** levels are usually elevated, although they are not specific to Hashimoto thyroiditis and are also seen in other autoimmune thyroid disorders (eg, postpartum thyroiditis, Graves disease).

If the diagnosis is uncertain (eg, thyroid nodularity), a biopsy can be performed to rule out malignancy. Characteristic findings of Hashimoto thyroiditis include a **lymphoplasmacytic infiltrate** with the formation of **germinal centers**. Residual follicles are often surrounded by Hürthle cells (large cells with granular, eosinophilic cytoplasm) representing follicular epithelial cells that have undergone metaplastic change in response to inflammation.

(Choice A) Histopathology in papillary thyroid carcinoma shows branching papillary structures with concentric calcifications (psammoma bodies) and ground-glass or empty-appearing nuclei ("Orphan Annie eye" nuclei). However, papillary thyroid carcinoma typically presents as an enlarging nodule in a clinically euthyroid patient.

(Choice B) Riedel thyroiditis is characterized by extensive fibrosis of the thyroid extending into the surrounding structures. The fibrotic gland is typically hard and fixed, often resembling a malignancy.

(Choice C) Graves disease presents with hyperthyroidism associated with a diffuse goiter, exophthalmos, and pretibial myxedema. Microscopy shows hyperplastic follicles with tall, crowded follicular epithelial cells projecting into the follicular lumen; hyperactive reabsorption causes scalloping around the edges of the colloid.

(Choice E) Subacute granulomatous (de Quervain/postviral) thyroiditis is characterized by the disruption of follicles and a mixed cellular infiltrate with occasional multinucleated giant cells. It typically presents after a viral upper respiratory infection with fever and a painful, tender thyroid.

Educational objective:
Chronic lymphocytic (Hashimoto) thyroiditis is a common cause of primary hypothyroidism. Histopathology findings include intense lymphoplasmacytic infiltrate, often with germinal centers. Residual follicles may be

https://t.me/USMLEWorldStep1

the United States.

In all forms of primary hypothyroidism, laboratory studies show low serum thyroxine (T4) levels and elevated TSH. **Antithyroid peroxidase antibody** levels are usually elevated, although they are not specific to Hashimoto thyroiditis and are also seen in other autoimmune thyroid disorders (eg, postpartum thyroiditis, Graves disease).

If the diagnosis is uncertain (eg, thyroid nodularity), a biopsy can be performed to rule out malignancy. Characteristic findings of Hashimoto thyroiditis include a **lymphoplasmacytic infiltrate** with the formation of **germinal centers**. Residual follicles are often surrounded by Hürthle cells (large cells with granular, eosinophilic cytoplasm) representing follicular epithelial cells that have undergone metaplastic change in response to inflammation.

(Choice A) Histopathology in papillary thyroid carcinoma shows branching papillary structures with concentric calcifications (psammoma bodies) and ground-glass or empty-appearing nuclei ("Orphan Annie eye" nuclei). However, papillary thyroid carcinoma typically presents as an enlarging nodule in a clinically euthyroid patient.

(Choice B) Riedel thyroiditis is characterized by extensive fibrosis of the thyroid extending into the surrounding structures. The fibrotic gland is typically hard and fixed, often resembling a malignancy.

(Choice C) Graves disease presents with hyperthyroidism associated with a diffuse goiter, exophthalmos, and pretibial myxedema. Microscopy shows hyperplastic follicles with tall, crowded follicular epithelial cells projecting into the follicular lumen; hyperactive reabsorption causes scalloping around the edges of the colloid.

(Choice E) Subacute granulomatous (de Quervain/postviral) thyroiditis is characterized by the disruption of follicles and a mixed cellular infiltrate with occasional multinucleated giant cells. It typically presents after a viral upper respiratory infection with fever and a painful, tender thyroid.

Educational objective:
Chronic lymphocytic (Hashimoto) thyroiditis is a common cause of primary hypothyroidism. Histopathology findings include intense lymphoplasmacytic infiltrate, often with germinal centers. Residual follicles may be surrounded by Hürthle cells (large cells with granular, eosinophilic cytoplasm).

Pathology	Endocrine, Diabetes & Metabolism	Hypothyroidism
Subject	System	Topic

https://t.me/USMLEWorldStep1

the United States.

In all f

Antith

thyroid

If the c

Chara

germi

cytopla

inflam

(Choi

calcific

Howev

(Choi

structu

(Choi

pretibi

into th

(Choi

follicle

upper

Educa

Chron

finding

surrou

Exhibit Display

Differential diagnosis of thyroiditis

Painful thyroiditis Pain & tenderness Systemic symptoms	**Painless thyroiditis** Autoimmune/+TPO antibody Destruction of follicles Release of preformed hormone & thyroglobulin	**Graves** +TSI/TRAb ↑ Thyroid hormone synthesis	**Fibrotic** Replacement of follicles with fibrotic tissue
Subacute (granulomatous, DeQuervain) • Tender goiter • Transient hyperthyroid phase • Postviral syndrome **Acute** (suppurative) • Fever • Asymmetry • Fluctuance	**Chronic lymphocytic** (Hashimoto) • Common • Usually hypothyroid at diagnosis **Postpartum** • ≤12 months after parturition • Transient hyperthyroid phase	**Graves disease** • Overt hyperthyroidism • ↑ RAIU • Ophthalmopathy	**Riedel thyroiditis** • Hard/fixed goiter • Compression of esophagus & trachea

TPO = thyroid peroxidase; **TSI** = thyroid-stimulating immunoglobulin;
TRAb = thyrotropin receptor antibody; **RAIU** = radioiodine uptake.

©UWorld

Zoom In Zoom Out Reset New | Existing My Notebook

Pathology (Subject) | Endocrine, Diabetes & Metabolism (System) | Hypothyroidism (Topic)

https://t.me/USMLEWorldStep1

the United States.

In all f

Antith

thyroid

If the c

Chara

germi

cytopla

inflam

(Choi

calcific

Howev

(Choi

structu

(Choi

pretibi

into th

(Choi

follicle

upper

Educa

Chron

finding

surrou

Exhibit Display

Differential diagnosis of thyroiditis

Painful thyroiditis Pain & tenderness Systemic symptoms	**Painless thyroiditis** Autoimmune/+TPO antibody Destruction of follicles Release of preformed hormone & thyroglobulin	**Graves** +TSI/TRAb ↑ Thyroid hormone synthesis	**Fibrotic** Replacement of follicles with fibrotic tissue
Subacute (granulomatous, DeQuervain) • Tender goiter • Transient hyperthyroid phase • Postviral syndrome **Acute** (suppurative) • Fever • Asymmetry • Fluctuance	**Chronic lymphocytic** (Hashimoto) • Common • Usually hypothyroid at diagnosis **Postpartum** • ≤12 months after parturition • Transient hyperthyroid phase	**Graves disease** • Overt hyperthyroidism • ↑ RAIU • Ophthalmopathy	**Riedel thyroiditis** • Hard/fixed goiter • Compression of esophagus & trachea

TPO = thyroid peroxidase; **TSI** = thyroid-stimulating immunoglobulin;
TRAb = thyrotropin receptor antibody; **RAIU** = radioiodine uptake.

©UWorld

Zoom In Zoom Out Reset New | Existing My Notebook

Pathology (Subject) | Endocrine, Diabetes & Metabolism (System) | Hypothyroidism (Topic)

https://t.me/USMLEWorldStep1

the United States.

In all f

Antith

thyroic

If the c

Chara

germi

cytopl

inflam

(Choi

calcifi

Howe

(Choi

structu

(Choi

pretibi

into th

(Choi

follicle

upper

Educa

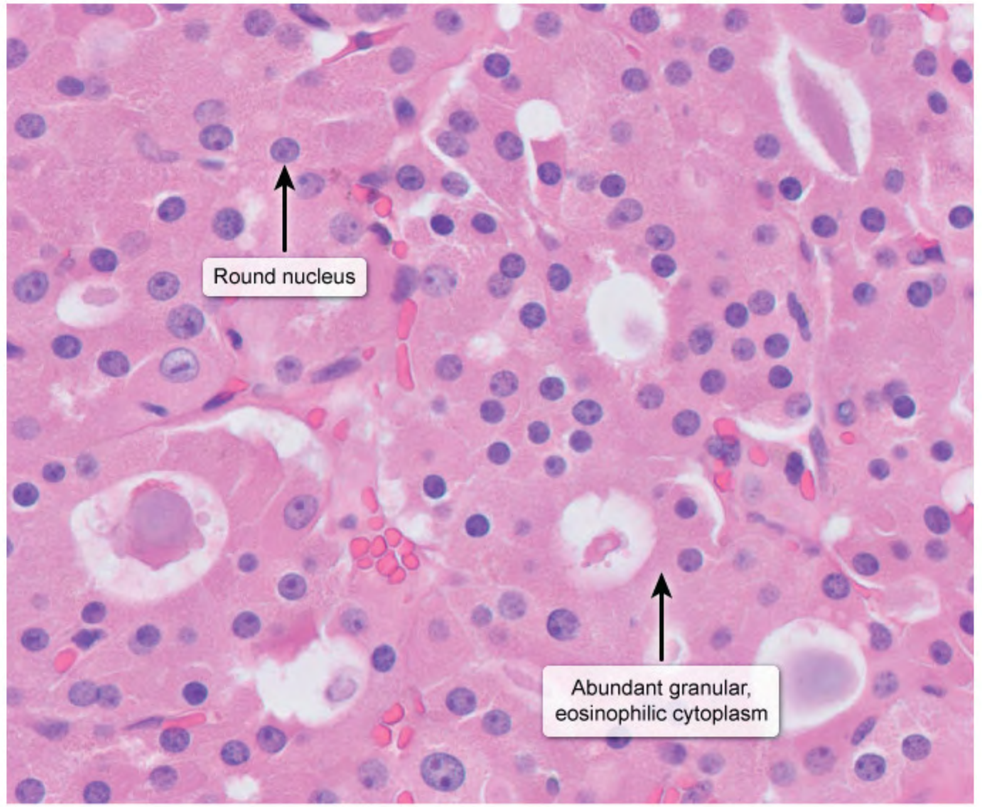
Chron

findin

surrou

Exhibit Display

Hürthle cells



©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Pathology	Endocrine, Diabetes & Metabolism	Hypothyroidism
Subject	System	Topic

https://t.me/USMLEWorldStep1

the United States.

In all f

Antith

thyroic

If the c

Chara

germi

cytopl

inflam

(Choi

calcifi

Howe

(Choi

structu

(Choi

pretibi

into th

(Choi

follicle

upper

Educa

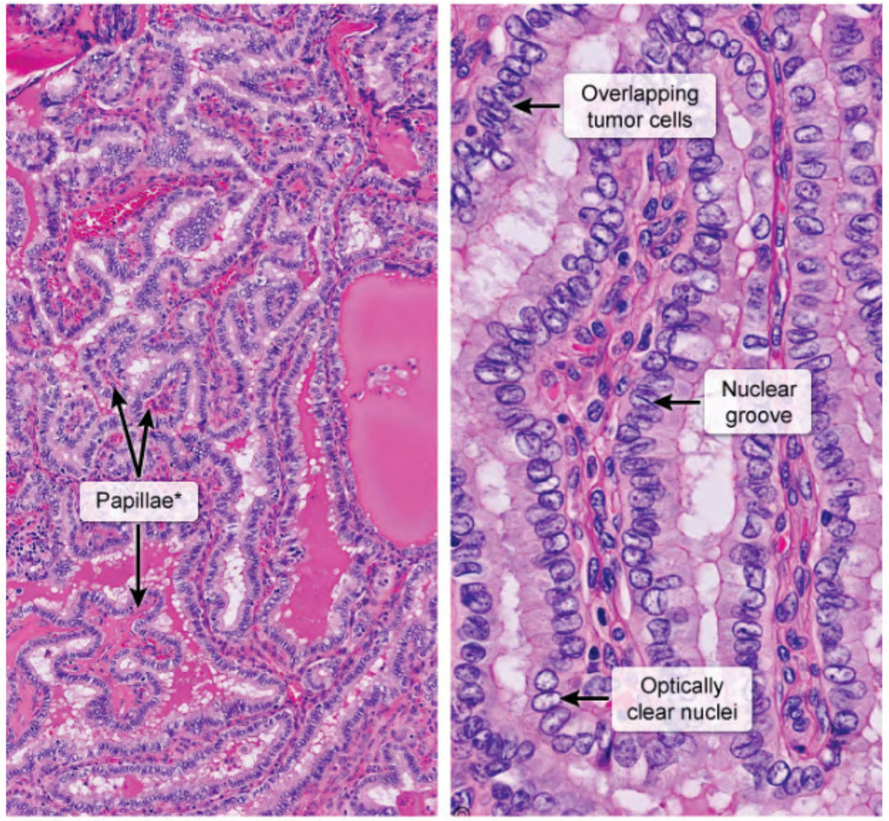
Chron

findin

surrou

Exhibit Display

Papillary thyroid carcinoma



*Fibrovascular cores lined by epithelial cells

©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Pathology	Endocrine, Diabetes & Metabolism	Hypothyroidism
Subject	System	Topic

https://t.me/USMLEWorldStep1

the United States.

In all f
Antith
thyroic

If the c
Chara
germi
cytopl
inflam

(Choi
calcifi
Howe

(Choi
structu

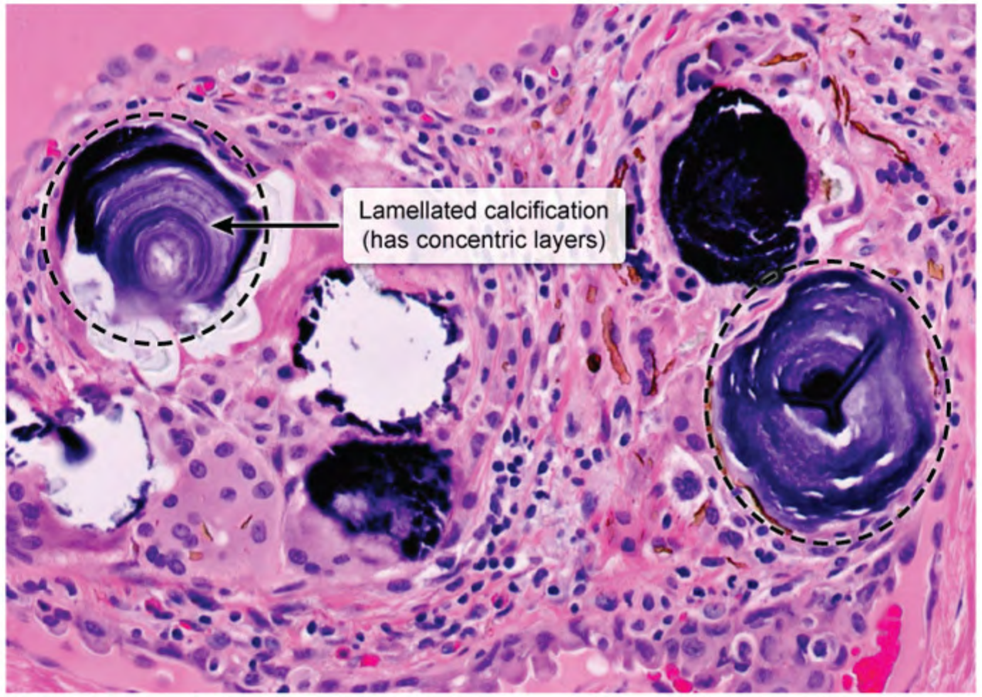
(Choi
pretibi
into th

(Choi
follicle
upper

Educa
Chron
findin
surrounded by Hurthle cells (large cells with granular, eosinophilic cytoplasm).

Exhibit Display

Psammoma bodies



©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Pathology	Endocrine, Diabetes & Metabolism	Hypothyroidism
Subject	System	Topic

https://t.me/USMLEWorldStep1

the United States.

In all f

Antith

thyroic

If the c

Chara

germi

cytopl

inflam

(Choi

calcifi

Howe

(Choi

structu

(Choi

pretibi

into th

(Choi

follicle

upper

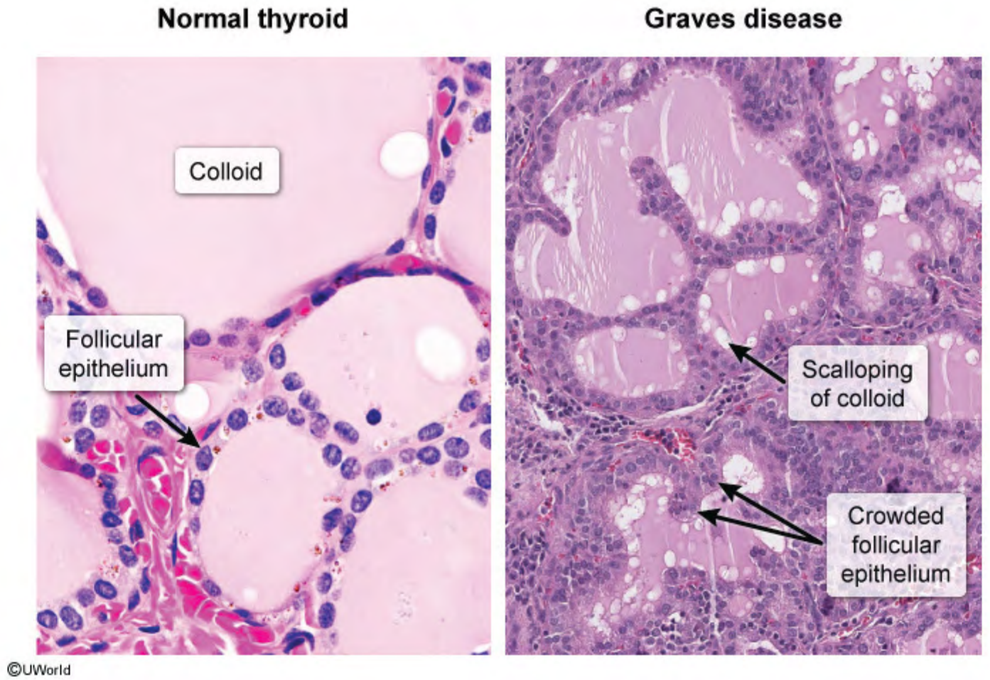
Educa

Chron

findin

surrou

Exhibit Display



Zoom In Zoom Out Reset New | Existing My Notebook

Pathology
Subject

Endocrine, Diabetes & Metabolism
System

Hypothyroidism
Topic

https://t.me/USMLEWorldStep1

A 13-year-old girl is brought to the clinic by her mother for a yearly physical examination. The patient feels well but is worried that she has not yet started puberty. Temperature is 36.7 C (98 F), blood pressure is 152/91 mm Hg, pulse is 75/min, and respirations are 18/min. Physical examination is significant for a lack of secondary sexual characteristics; a blind vagina is noted on pelvic examination. Laboratory studies reveal hypokalemia and low testosterone and estradiol levels. Cytogenetic analysis shows a 46,XY karyotype. This patient most likely has deficiency of which of the following enzymes?

- A. 5 alpha-reductase
- B. 11 beta-hydroxylase
- C. 17 alpha-hydroxylase
- D. 20,22-desmolase
- E. 21-hydroxylase

Submit

https://t.me/USMLEWorldStep1

A 13-year-old girl is brought to the clinic by her mother for a yearly physical examination. The patient feels well but is worried that she has not yet started puberty. Temperature is 36.7 C (98 F), blood pressure is 152/91 mm Hg, pulse is 75/min, and respirations are 18/min. Physical examination is significant for a lack of secondary sexual characteristics; a blind vagina is noted on pelvic examination. Laboratory studies reveal hypokalemia and low testosterone and estradiol levels. Cytogenetic analysis shows a 46,XY karyotype. This patient most likely has deficiency of which of the following enzymes?

- ✗ A. 5 alpha-reductase (11%)
- B. 11 beta-hydroxylase (11%)
- ✓ C. 17 alpha-hydroxylase (66%)
- D. 20,22-desmolase (2%)
- E. 21-hydroxylase (8%)

Incorrect
Correct answer
C

66%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

Congenital adrenal hyperplasia				
Enzyme deficiency	**Mineralocorticoids**	**Glucocorticoids**	**Androgens**	**Symptoms**
21-Hydroxylase	↓	↓	↑	• Salt wasting (vomiting, hypotension, ↓ Na^+, ↑ K^+) • Ambiguous genitalia in girls
11β-				• Hypertension, ↓ K^+

https://t.me/USMLEWorldStep1

Congenital adrenal hyperplasia				
Enzyme deficiency	**Mineralocorticoids**	**Glucocorticoids**	**Androgens**	**Symptoms**
21-Hydroxylase	↓	↓	↑	• Salt wasting (vomiting, hypotension, ↓ Na^+, ↑ K^+) • Ambiguous genitalia in girls
11β-Hydroxylase	↑*	↓	↑	• Hypertension, ↓ K^+ • Ambiguous genitalia in girls
17α-Hydroxylase	↑	↑**	↓	• Hypertension, ↓ K^+ • Ambiguous genitalia in boys • Absent puberty
*Low aldosterone but excessive, weak mineralocorticoid (11-deoxycorticosterone). **Low cortisol but excessive, weak glucocorticoid (corticosterone).				

This patient is genetically male (46,XY) with features suggestive of 17 alpha-hydroxylase deficiency, a rare cause of **congenital adrenal hyperplasia** (CAH). The enzyme 17 alpha-hydroxylase is active in the adrenal glands and gonads and is responsible for converting pregnenolone to 17-hydroxypregnenolone and progesterone to 17-hydroxyprogesterone. Deficiency of this enzyme **impairs synthesis of sex hormones** (eg, testosterone, estradiol) and cortisol but **does not inhibit mineralocorticoid production**.

Due to the absence of androgens in utero, genetic males (46,XY) with 17 alpha-hydroxylase deficiency have undervirilized, ambiguous genitalia. In severe cases, they appear **phenotypically female** but lack internal female genitalia, as in this case. In contrast, genetic females (46,XX) develop normal internal and external genitalia. At puberty, impaired synthesis of sex hormones in the gonads leads to **absent secondary sexual characteristics** in both sexes and primary amenorrhea in girls.

Excess mineralocorticoid production results in **hypertension** and **hypokalemia** that are usually detected around the expected time of **puberty**. Low cortisol provides positive feedback to increase ACTH production, further

https://t.me/USMLEWorldStep1

*Low aldosterone but excessive, weak mineralocorticoid (11-deoxycorticosterone).
**Low cortisol but excessive, weak glucocorticoid (corticosterone).

This patient is genetically male (46,XY) with features suggestive of 17 alpha-hydroxylase deficiency, a rare cause of **congenital adrenal hyperplasia** (CAH). The enzyme 17 alpha-hydroxylase is active in the adrenal glands and gonads and is responsible for converting pregnenolone to 17-hydroxypregnenolone and progesterone to 17-hydroxyprogesterone. Deficiency of this enzyme **impairs synthesis of sex hormones** (eg, testosterone, estradiol) and cortisol but **does not inhibit mineralocorticoid production**.

Due to the absence of androgens in utero, genetic males (46,XY) with 17 alpha-hydroxylase deficiency have undervirilized, ambiguous genitalia. In severe cases, they appear **phenotypically female** but lack internal female genitalia, as in this case. In contrast, genetic females (46,XX) develop normal internal and external genitalia. At puberty, impaired synthesis of sex hormones in the gonads leads to **absent secondary sexual characteristics** in both sexes and primary amenorrhea in girls.

Excess mineralocorticoid production results in **hypertension** and **hypokalemia** that are usually detected around the expected time of **puberty**. Low cortisol provides positive feedback to increase ACTH production, further stimulating the mineralocorticoid pathway. This allows for the excess production of weak glucocorticoids (ie, corticosterone), preventing the detrimental effects of low cortisol.

(Choice A) 5 alpha-reductase deficiency prevents conversion of testosterone to dihydrotestosterone, the hormone responsible for male external genitalia development. Affected genetic males have ambiguous genitalia at birth but develop normal secondary sexual characteristics (eg, increased muscle mass, phallus enlargement) at puberty because these features are testosterone dependent. Blood pressure and electrolytes are unaffected.

(Choice B) 11 beta-hydroxylase deficiency causes decreased glucocorticoid synthesis and increased production of adrenal androgens. Because the production of 11-deoxycorticosterone (weak mineralocorticoid) is also increased, individuals with this deficiency have features of mineralocorticoid excess (eg, hypertension, hypokalemia). However, genetic males appear phenotypically normal.

(Choice D) 20,22-desmolase (side chain cleavage enzyme) deficiency results in impaired synthesis of all steroid hormones with accumulation of cholesterol esters in the adrenal glands and gonads. Complete deficiency is lethal,

https://t.me/USMLEWorldStep1

genitalia, as in this case. In contrast, genetic females (46,XX) develop normal internal and external genitalia. At puberty, impaired synthesis of sex hormones in the gonads leads to **absent secondary sexual characteristics** in both sexes and primary amenorrhea in girls.

Excess mineralocorticoid production results in **hypertension** and **hypokalemia** that are usually detected around the expected time of **puberty**. Low cortisol provides positive feedback to increase ACTH production, further stimulating the mineralocorticoid pathway. This allows for the excess production of weak glucocorticoids (ie, corticosterone), preventing the detrimental effects of low cortisol.

(Choice A) 5 alpha-reductase deficiency prevents conversion of testosterone to dihydrotestosterone, the hormone responsible for male external genitalia development. Affected genetic males have ambiguous genitalia at birth but develop normal secondary sexual characteristics (eg, increased muscle mass, phallus enlargement) at puberty because these features are testosterone dependent. Blood pressure and electrolytes are unaffected.

(Choice B) 11 beta-hydroxylase deficiency causes decreased glucocorticoid synthesis and increased production of adrenal androgens. Because the production of 11-deoxycorticosterone (weak mineralocorticoid) is also increased, individuals with this deficiency have features of mineralocorticoid excess (eg, hypertension, hypokalemia). However, genetic males appear phenotypically normal.

(Choice D) 20,22-desmolase (side chain cleavage enzyme) deficiency results in impaired synthesis of all steroid hormones with accumulation of cholesterol esters in the adrenal glands and gonads. Complete deficiency is lethal, and partial deficiency typically presents in infancy with signs of adrenal insufficiency (eg, hypotension, hyperkalemia).

(Choice E) The most common form of CAH is 21-hydroxylase deficiency. It causes decreased glucocorticoid and mineralocorticoid synthesis and increased adrenal androgen production. In contrast to this patient, genetic males with 21-hydroxylase deficiency appear phenotypically normal.

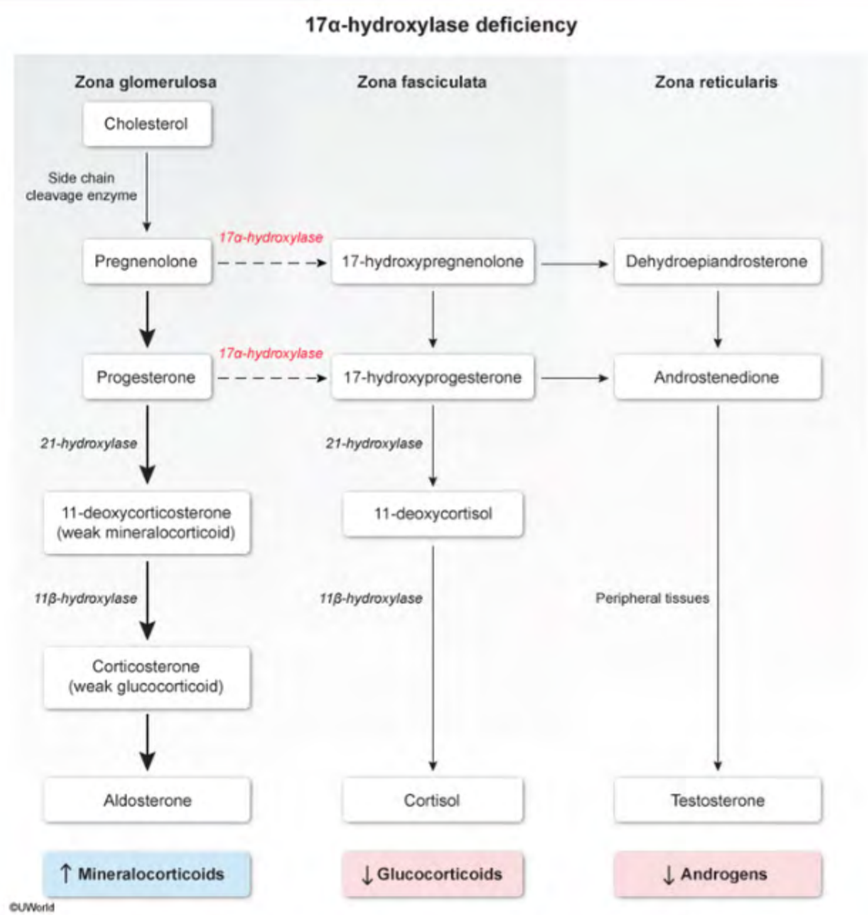
Educational objective:
Deficiency of 17 alpha-hydroxylase is a rare form of congenital adrenal hyperplasia characterized by impaired synthesis of androgens, estrogens, and cortisol with excess production of mineralocorticoids. Genetic males with this deficiency may have phenotypically female external genitalia and present with hypertension and hypokalemia around the expected time of puberty.

https://t.me/USMLEWorldStep1

*Low aldosterone but excessive, weak mineralocorticoid (11-deoxycorticosterone).

**L

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

This p
of **con**
gonad
hydrox
estrad

Due to
underv
genita
pubert
both s

Exces
the ex
stimul
cortico

(Choi
respon
develo
becau

(Choi
of adre
increa
hypok

(Choi

hormones with accumulation of cholesterol esters in the adrenal glands and gonads. Complete deficiency is lethal,

https://t.me/USMLEWorldStep1

*Low aldosterone but excessive, weak mineralocorticoid (11-deoxycorticosterone).

**L

Exhibit Display

This p
of **con**
gonad
hydrox
estrad

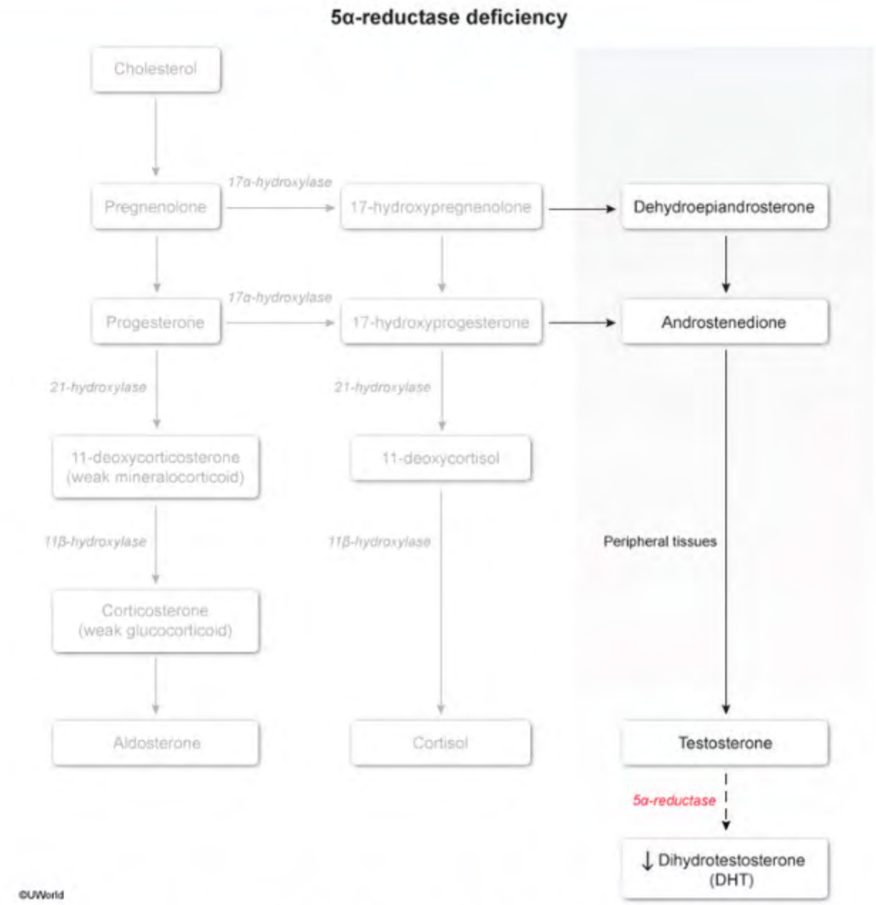
Due to
underv
genita
pubert
both s

Exces
the ex
stimul
cortico

(Choi
respon
develo
becau

(Choi
of adre
increa
hypok

(Choi



Zoom In Zoom Out Reset New | Existing My Notebook

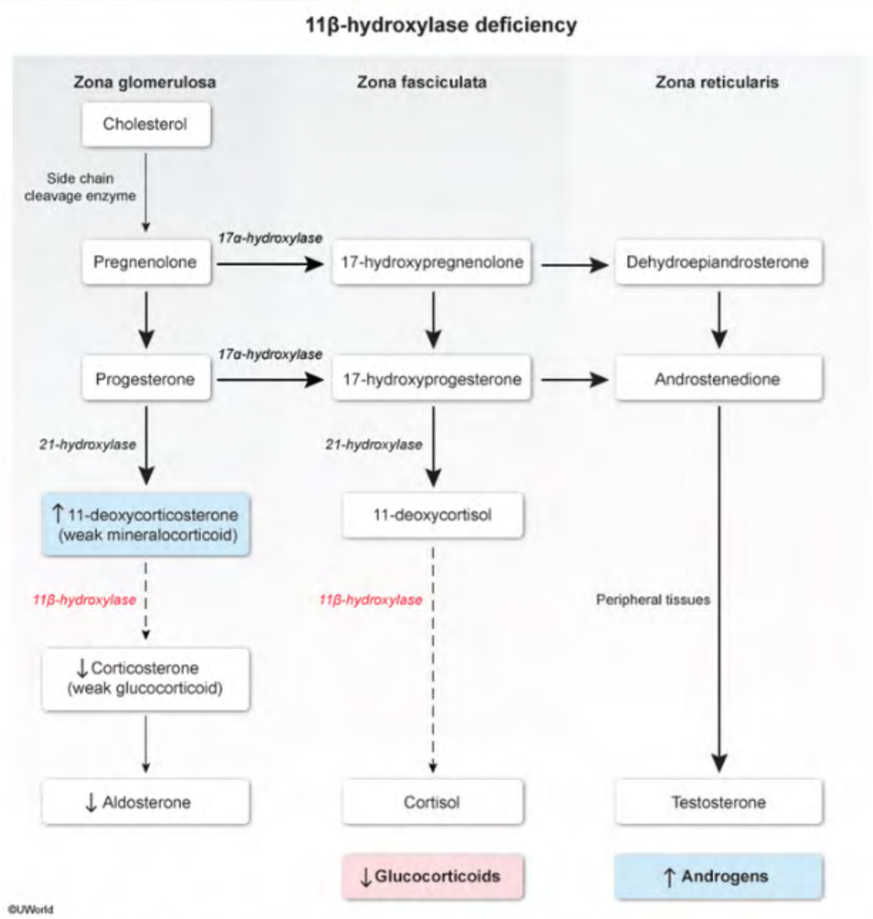
hormones with accumulation of cholesterol esters in the adrenal glands and gonads. Complete deficiency is lethal,

https://t.me/USMLEWorldStep1

*Low aldosterone but excessive, weak mineralocorticoid (11-deoxycorticosterone).

**L

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

This p
of **con**
gonad
hydrox
estrad

Due to
underv
genita
pubert
both s

Exces
the ex
stimul
cortico

(Choi
respon
develo
becau

(Choi
of adre
increa
hypok

(Choi
hormones with accumulation of cholesterol esters in the adrenal glands and gonads. Complete deficiency is lethal,

https://t.me/USMLEWorldStep1

estradiol) and cortisol but **does not inhibit mineralocorticoid production**.

Due to
underv
genita
pubert
both s

Exces
the ex
stimula
cortico

(Choi
respor
develo
becau

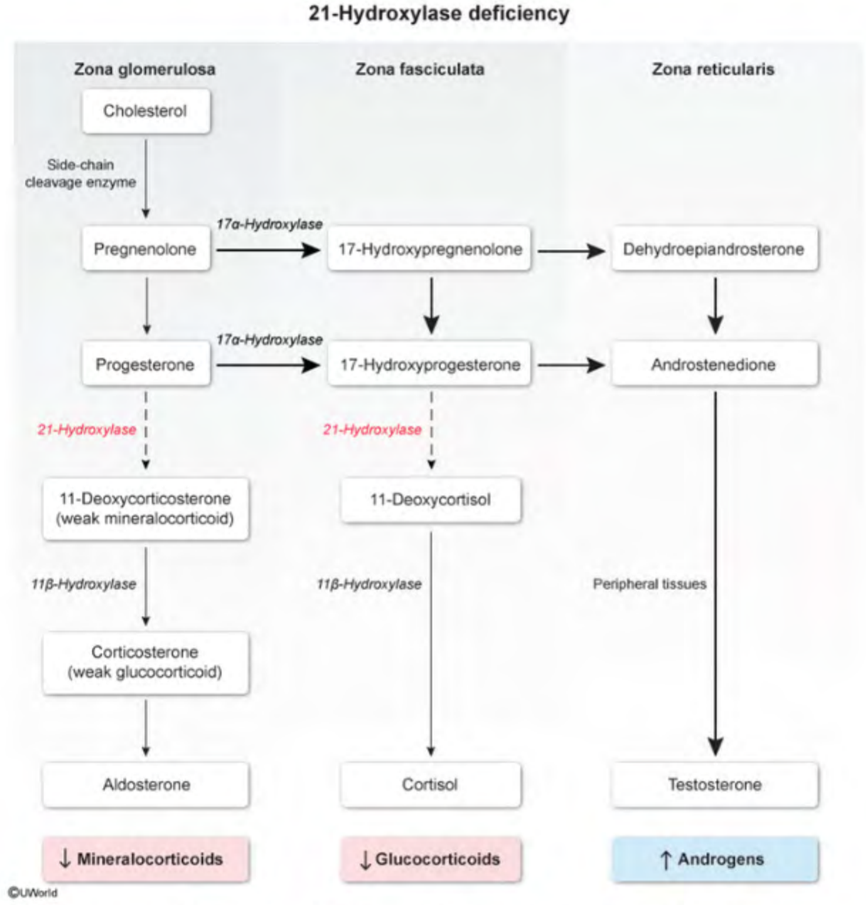
(Choi
of adre
increa
hypok

(Choi
hormo
and pa
hyperk

(Choi
minera
with 2

Educational objective:

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

A 29-year-old woman comes to the office due to unintentional weight loss, fatigue, and sweating. The patient has had no neck pain. Two months ago, she delivered a healthy boy with no perinatal complications. The patient does not breastfeed the infant. She has no chronic medical conditions and takes no medications. Blood pressure is 140/70 mm Hg, pulse is 110/min, and respirations are 16/min. Oxygen saturation is 98% on room air. Neck examination shows mild, diffuse enlargement of the thyroid gland with no tenderness. The remainder of the physical examination, including pelvic examination, is normal. Laboratory evaluation reveals low serum TSH, elevated serum thyroxine (T4), and elevated serum triiodothyronine (T3). Thyrotropin receptor antibodies are negative. Which of the following is the most likely cause of this patient's symptoms?

- A. Exogenous intake of thyroid hormone
- B. Granulomatous inflammation of the thyroid gland
- C. Lymphocytic inflammation of the pituitary gland
- D. Lymphocytic inflammation of the thyroid gland
- E. Tumor production of β-hCG

Submit

https://t.me/USMLEWorldStep1

A 29-year-old woman comes to the office due to unintentional weight loss, fatigue, and sweating. The patient has had no neck pain. Two months ago, she delivered a healthy boy with no perinatal complications. The patient does not breastfeed the infant. She has no chronic medical conditions and takes no medications. Blood pressure is 140/70 mm Hg, pulse is 110/min, and respirations are 16/min. Oxygen saturation is 98% on room air. Neck examination shows mild, diffuse enlargement of the thyroid gland with no tenderness. The remainder of the physical examination, including pelvic examination, is normal. Laboratory evaluation reveals low serum TSH, elevated serum thyroxine (T4), and elevated serum triiodothyronine (T3). Thyrotropin receptor antibodies are negative. Which of the following is the most likely cause of this patient's symptoms?

- A. Exogenous intake of thyroid hormone (14%)
- ✗ B. Granulomatous inflammation of the thyroid gland (13%)
- C. Lymphocytic inflammation of the pituitary gland (4%)
- ✓ D. Lymphocytic inflammation of the thyroid gland (53%)
- E. Tumor production of β-hCG (14%)

Incorrect
Correct answer
D

53%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

Postpartum thyroiditis	
Pathophysiology	• Autoimmune destruction of thyroid follicles & release of preformed thyroid hormone • Lymphocytic infiltrates ± germinal centers
Clinical course	• Onset ≤12 months after pregnancy • Transient hyperthyroid phase (↑ T4 & T3, ↓ TSH)

https://t.me/USMLEWorldStep1

Explanation

Postpartum thyroiditis	
Pathophysiology	• Autoimmune destruction of thyroid follicles & release of preformed thyroid hormone • Lymphocytic infiltrates ± germinal centers
Clinical course	• Onset ≤12 months after pregnancy • Transient hyperthyroid phase (↑ T4 & T3, ↓ TSH) • Brief hypothyroid phase (↓ T4 & T3, ↑ TSH) • Return to euthyroid state
Diagnosis	• ↑ Serum thyroglobulin • ↓ Radioiodine uptake • Ultrasound: diffuse thyroid enlargement with ↓ blood flow
T3 = triiodothyronine; **T4** = thyroxine.	

This patient has weight loss, tachycardia, and a painless, diffuse goiter; her serum thyroid hormone levels are elevated and TSH is suppressed, findings consistent with **primary hyperthyroidism**. In light of her recent pregnancy and negative thyrotropin receptor antibody assay (which makes Graves disease unlikely) this is most likely due to **postpartum thyroiditis**.

Postpartum thyroiditis occurs within 12 months of pregnancy and is characterized by **autoimmune destruction of thyroid follicles** similar to that seen in chronic lymphocytic (Hashimoto) thyroiditis. Histologic inspection demonstrates **lymphocytic infiltration**, sometimes with the formation of germinal centers. The breakdown of follicle margins and loss of colloid may also be seen.

Postpartum thyroiditis typically begins with a hyperthyroid phase due to the **release of preformed thyroid hormone**, followed by a transient hypothyroid phase due to the depletion of thyroid hormone and an eventual return to a euthyroid state.

(Choice A) Intake of exogenous thyroid hormone can cause thyrotoxicosis with suppression of TSH. However,

https://t.me/USMLEWorldStep1

This patient has weight loss, tachycardia, and a painless, diffuse goiter; her serum thyroid hormone levels are elevated and TSH is suppressed, findings consistent with **primary hyperthyroidism**. In light of her recent pregnancy and negative thyrotropin receptor antibody assay (which makes Graves disease unlikely) this is most likely due to **postpartum thyroiditis**.

Postpartum thyroiditis occurs within 12 months of pregnancy and is characterized by **autoimmune destruction of thyroid follicles** similar to that seen in chronic lymphocytic (Hashimoto) thyroiditis. Histologic inspection demonstrates **lymphocytic infiltration**, sometimes with the formation of germinal centers. The breakdown of follicle margins and loss of colloid may also be seen.

Postpartum thyroiditis typically begins with a hyperthyroid phase due to the **release of preformed thyroid hormone**, followed by a transient hypothyroid phase due to the depletion of thyroid hormone and an eventual return to a euthyroid state.

(Choice A) Intake of exogenous thyroid hormone can cause thyrotoxicosis with suppression of TSH. However, thyroid enlargement would not be seen (thyroid atrophy is more typical).

(Choice B) Like postpartum thyroiditis, subacute granulomatous (de Quervain/postviral) thyroiditis can have a transient hyperthyroid phase due to the release of preformed thyroid hormone. However, patients typically have low-grade fever, myalgias, and a painful, tender goiter.

(Choice C) Lymphocytic hypophysitis is an uncommon disorder that may occur in postpartum women. TSH would be low due to loss of pituitary thyrotrophs, but thyroid hormone levels would also be low (ie, central/secondary hypothyroidism).

(Choice E) The beta subunit of hCG shares homology with TSH and can stimulate TSH receptors on follicular cells. Gestational trophoblastic neoplasia refers to a group of hCG-secreting tumors that most commonly occur in association with molar pregnancy (uncommon following live birth). Most patients have associated symptoms such as amenorrhea or abnormal uterine bleeding, and examination often shows uterine enlargement.

Educational objective:
Postpartum thyroiditis occurs within 12 months of pregnancy and is characterized by autoimmune destruction of thyroid follicles. It typically begins with a hyperthyroid phase due to the release of preformed thyroid hormone,

https://t.me/USMLEWorldStep1

likely due to **postpartum thyroiditis**.

Postpartum thyroiditis occurs within 12 months of pregnancy and is characterized by **autoimmune destruction of thyroid follicles** similar to that seen in chronic lymphocytic (Hashimoto) thyroiditis. Histologic inspection demonstrates **lymphocytic infiltration**, sometimes with the formation of germinal centers. The breakdown of follicle margins and loss of colloid may also be seen.

Postpartum thyroiditis typically begins with a hyperthyroid phase due to the **release of preformed thyroid hormone**, followed by a transient hypothyroid phase due to the depletion of thyroid hormone and an eventual return to a euthyroid state.

(Choice A) Intake of exogenous thyroid hormone can cause thyrotoxicosis with suppression of TSH. However, thyroid enlargement would not be seen (thyroid atrophy is more typical).

(Choice B) Like postpartum thyroiditis, subacute granulomatous (de Quervain/postviral) thyroiditis can have a transient hyperthyroid phase due to the release of preformed thyroid hormone. However, patients typically have low-grade fever, myalgias, and a painful, tender goiter.

(Choice C) Lymphocytic hypophysitis is an uncommon disorder that may occur in postpartum women. TSH would be low due to loss of pituitary thyrotrophs, but thyroid hormone levels would also be low (ie, central/secondary hypothyroidism).

(Choice E) The beta subunit of hCG shares homology with TSH and can stimulate TSH receptors on follicular cells. Gestational trophoblastic neoplasia refers to a group of hCG-secreting tumors that most commonly occur in association with molar pregnancy (uncommon following live birth). Most patients have associated symptoms such as amenorrhea or abnormal uterine bleeding, and examination often shows uterine enlargement.

Educational objective:
Postpartum thyroiditis occurs within 12 months of pregnancy and is characterized by autoimmune destruction of thyroid follicles. It typically begins with a hyperthyroid phase due to the release of preformed thyroid hormone, followed by a hypothyroid phase due to depletion of thyroid hormone and an eventual return to a euthyroid state. Histologic inspection demonstrates lymphocytic infiltration with the formation of germinal centers, which is similar to chronic lymphocytic (Hashimoto) thyroiditis.

https://t.me/USMLEWorldStep1

- Ultrasound: diffuse thyroid enlargement with ↓ blood flow

Exhibit Display

Differential diagnosis of thyroiditis

Painful thyroiditis Pain & tenderness Systemic symptoms	**Painless thyroiditis** Autoimmune/+TPO antibody Destruction of follicles Release of preformed hormone & thyroglobulin	**Graves** +TSI/TRAb ↑ Thyroid hormone synthesis	**Fibrotic** Replacement of follicles with fibrotic tissue
Subacute (granulomatous, DeQuervain) • Tender goiter • Transient hyperthyroid phase • Postviral syndrome **Acute** (suppurative) • Fever • Asymmetry • Fluctuance	**Chronic lymphocytic** (Hashimoto) • Common • Usually hypothyroid at diagnosis **Postpartum** • ≤12 months after parturition • Transient hyperthyroid phase	**Graves disease** • Overt hyperthyroidism • ↑ RAIU • Ophthalmopathy	**Riedel thyroiditis** • Hard/fixed goiter • Compression of esophagus & trachea

TPO = thyroid peroxidase; **TSI** = thyroid-stimulating immunoglobulin; **TRAb** = thyrotropin receptor antibody; **RAIU** = radioiodine uptake.

©UWorld

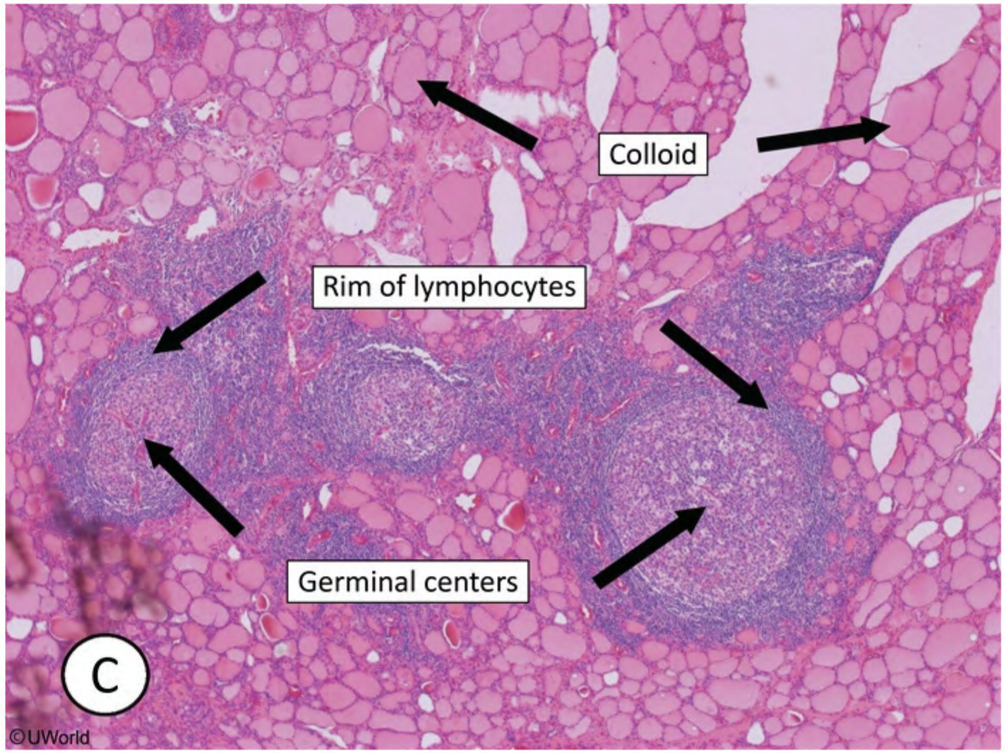
Zoom In Zoom Out Reset New | Existing My Notebook

as amenorrhea or abnormal uterine bleeding, and examination often shows uterine enlargement.

https://t.me/USMLEWorldStep1

- Ultrasound: diffuse thyroid enlargement with ↓ blood flow

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

This p
elevat
pregna
likely c

Postpa
thyroi
demor
follicle

Postpa
hormo
return

(Choi
thyroic

(Choi
transie
low-gr

(Choi
be low
hypoth

(Choi
cells.
associ
as amenorrhea or abnormal uterine bleeding, and examination often shows uterine enlargement.

https://t.me/USMLEWorldStep1

A study is conducted to assess the effect of parathyroid hormone (PTH) on bone remodeling. Half of the study subjects receive intermittent PTH injections and the other half receive a continuous infusion of PTH. The results show that the effects on bone metabolism of intermittent PTH injections are different from those of continuous infusion. Which of the following is most likely to be the predominant bone effect with intermittent injections?

- A. Increased activity of matrix metalloproteinases
- B. Increased levels of osteoprotegerin
- C. Osteoclast apoptosis
- D. Stimulation of osteoblast activity
- E. Suppression of RANK and RANK-ligand activity

Submit

https://t.me/USMLEWorldStep1

A study is conducted to assess the effect of parathyroid hormone (PTH) on bone remodeling. Half of the study subjects receive intermittent PTH injections and the other half receive a continuous infusion of PTH. The results show that the effects on bone metabolism of intermittent PTH injections are different from those of continuous infusion. Which of the following is most likely to be the predominant bone effect with intermittent injections?

- A. Increased activity of matrix metalloproteinases (11%)
- ✗ B. Increased levels of osteoprotegerin (7%)
- C. Osteoclast apoptosis (2%)
- ✓ D. Stimulation of osteoblast activity (69%)
- E. Suppression of RANK and RANK-ligand activity (8%)

Incorrect
Correct answer
D

69%
Answered correctly

04 secs
Time Spent

2023
Version

Explanation

Parathyroid hormone (PTH) is secreted in response to low circulating calcium levels. It has a very short half-life (<5 min) and is released in a combination continuous/tonic and pulsatile pattern (approximately two-thirds tonic secretion, one-third pulsatile). PTH supports plasma calcium levels by increasing intestinal calcium absorption, renal calcium reabsorption, and release of calcium from bone stores. Continuous high levels of PTH (ie, hyperparathyroidism) lead to excessive release of calcium from bones and increase the risk of osteoporosis.

However, **pulsatile PTH secretion** has an anabolic effect on bone metabolism, **stimulating osteoblast proliferation**, decreasing osteoblast apoptosis, and inducing **increased formation of new bone**. Recombinant PTH analogues (eg, teriparatide) are used to treat severe osteoporosis; these analogues promote bone remodeling by inducing increased resorption of old bone while stimulating a corresponding increase in new bone production, resulting in a net increase in total bone mass (ie, **positive bone balance**).

https://t.me/USMLEWorldStep1

Parathyroid hormone (PTH) is secreted in response to low circulating calcium levels. It has a very short half-life (<5 min) and is released in a combination continuous/tonic and pulsatile pattern (approximately two-thirds tonic secretion, one-third pulsatile). PTH supports plasma calcium levels by increasing intestinal calcium absorption, renal calcium reabsorption, and release of calcium from bone stores. Continuous high levels of PTH (ie, hyperparathyroidism) lead to excessive release of calcium from bones and increase the risk of osteoporosis.

However, **pulsatile PTH secretion** has an anabolic effect on bone metabolism, **stimulating osteoblast proliferation**, decreasing osteoblast apoptosis, and inducing **increased formation of new bone**. Recombinant PTH analogues (eg, teriparatide) are used to treat severe osteoporosis; these analogues promote bone remodeling by inducing increased resorption of old bone while stimulating a corresponding increase in new bone production, resulting in a net increase in total bone mass (ie, **positive bone balance**).

(Choice A) Matrix metalloproteinases (MMPs) are a family of enzymes involved in the turnover of connective tissue proteins in the extracellular matrix. Multiple MMPs are produced by osteoclasts and are involved in the breakdown of bone matrix. In general, intermittent PTH has more effect on bone formation, with minimal increase in osteoclast/MMP activity.

(Choices B and C) High estrogen levels in premenopausal women delay the onset of osteoporosis by suppressing bone resorption. This effect is mediated largely by osteoprotegerin, which induces apoptosis of osteoclasts by acting as a decoy receptor to the receptor activator of nuclear factor kappa B (RANK)/RANK-ligand interaction.

(Choice E) Binding of PTH to PTH receptor type 1 on osteoblasts increases (not suppresses) the expression of RANK-ligand, which subsequently interacts with RANK on osteoclast precursors to promote osteoclast differentiation and suppress osteoclast apoptosis.

Educational objective:
Parathyroid hormone (PTH) is released in a combination continuous/tonic and pulsatile pattern. Continuous high levels of PTH lead to excessive release of calcium from bones and increase the risk of osteoporosis; however, pulsatile secretion has an anabolic effect on bone metabolism, stimulating osteoblast proliferation and inducing increased formation of new bone.

https://t.me/USMLEWorldStep1

Parathyroid hormone (PTH) is secreted in response to low circulating calcium levels. It has a very short half-life (<5 mi
secret
renal c
hyperp

Howev
prolife
PTH a
by ind
resulti

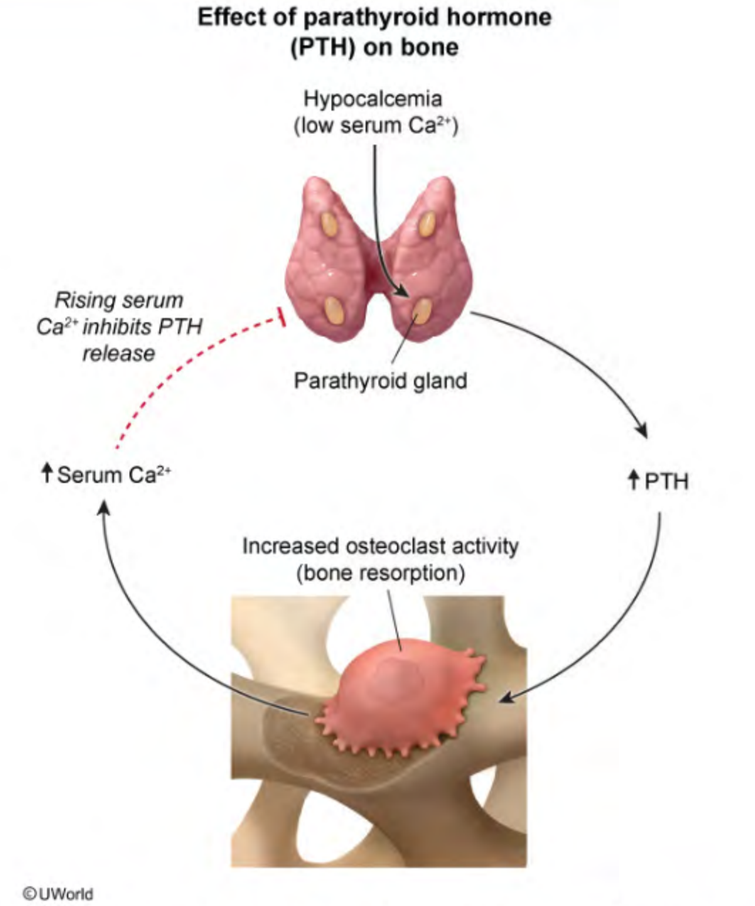
(Choi
tissue
breako
in oste

(Choi
suppre
osteoc
interac

(Choi
RANK
differe

Educa
Parath
levels
pulsati
increased formation of new bone.

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

renal calcium reabsorption, and release of calcium from bone stores. Continuous high levels of PTH (ie,
hyperparathyroidism) lead to excessive release of calcium from bones and increase the risk of osteoporosis.

Howev
prolife
PTH a
by ind
resulti

(Choi
tissue
breako
in oste

(Choi
suppre
osteoc
interac

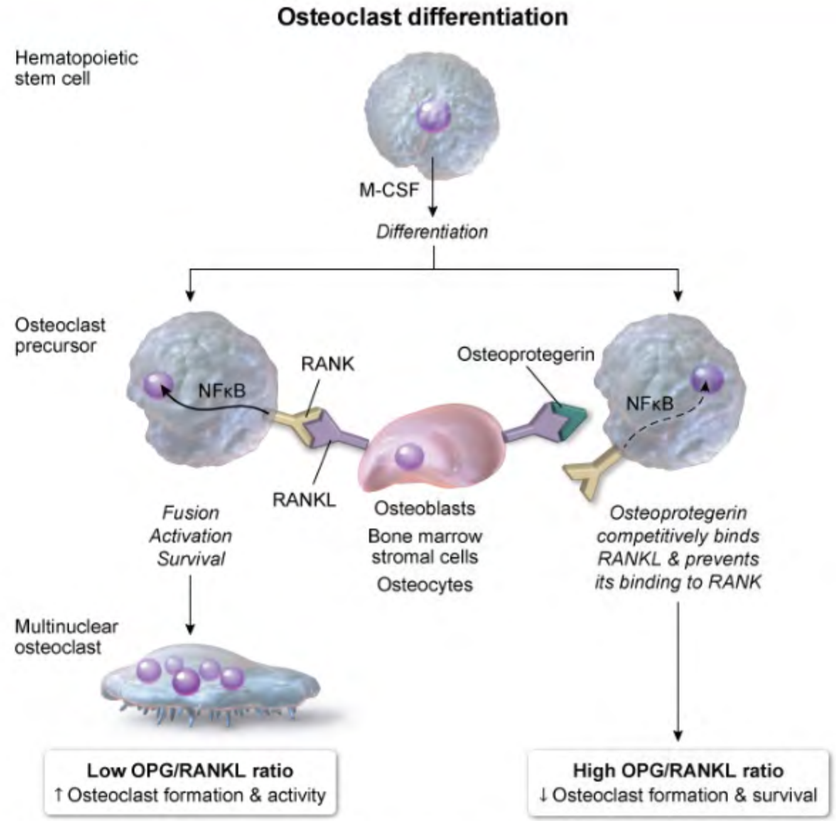
(Choi
RANK
differe

Educa
Parath
levels
pulsati
increa

Refere
- Bo

Pharmacology Endocrine, Diabetes & Metabolism Osteoporosis

Exhibit Display



Zoom In Zoom Out Reset New | Existing My Notebook

https://t.me/USMLEWorldStep1

A 22-year-old woman comes to the emergency department due to fatigue and sore throat for the past few days. The throat discomfort has caused her to be unable to eat or drink without significant pain. Acetaminophen improves the pain slightly, but her oral intake has been poor. The patient recently started taking antithyroid medication for Graves disease. She has no other medical conditions and does not use tobacco, alcohol, or recreational drugs. Weight is 67 kg (148 lb), decreased from 68.5 kg (151 lb) a week ago. Temperature is 38.9 C (102 F), blood pressure is 102/68 mm Hg, and pulse is 130/min. Physical examination shows an erythematous pharynx with shallow mucosal ulcerations and a normal-sized thyroid. Mucous membranes appear dry. The abdomen is soft and nontender. No tremor is seen with outstretching of the hands. Which of the following is the most likely cause of this patient's current condition?

- A. Acute adrenal insufficiency
- B. Drug-induced granulocyte destruction
- C. Excessive thyroid suppression
- D. Thyroid hormone–induced severe hypermetabolism
- E. Virus-induced lymphocyte destruction

Submit

https://t.me/USMLEWorldStep1

A 22-year-old woman comes to the emergency department due to fatigue and sore throat for the past few days. The throat discomfort has caused her to be unable to eat or drink without significant pain. Acetaminophen improves the pain slightly, but her oral intake has been poor. The patient recently started taking antithyroid medication for Graves disease. She has no other medical conditions and does not use tobacco, alcohol, or recreational drugs. Weight is 67 kg (148 lb), decreased from 68.5 kg (151 lb) a week ago. Temperature is 38.9 C (102 F), blood pressure is 102/68 mm Hg, and pulse is 130/min. Physical examination shows an erythematous pharynx with shallow mucosal ulcerations and a normal-sized thyroid. Mucous membranes appear dry. The abdomen is soft and nontender. No tremor is seen with outstretching of the hands. Which of the following is the most likely cause of this patient's current condition?

- ✗ A. Acute adrenal insufficiency (3%)
- ✓ B. Drug-induced granulocyte destruction (52%)
- C. Excessive thyroid suppression (9%)
- D. Thyroid hormone–induced severe hypermetabolism (10%)
- E. Virus-induced lymphocyte destruction (25%)

Incorrect
Correct answer
B

52%
Answered correctly

04 secs
Time Spent

2023
Version

Explanation

Medications associated with drug-induced neutropenia	
Antithyroid	• Methimazole • Propylthiouracil
Anti-inflammatory	• Sulfasalazine

https://t.me/USMLEWorldStep1

Medications associated with drug-induced neutropenia	
Antithyroid	• Methimazole • Propylthiouracil
Anti-inflammatory	• Sulfasalazine • Methotrexate
Psychotropic or anticonvulsant	• Clozapine • Carbamazepine • Phenytoin
Cardiovascular	• Antiarrhythmic agents (eg, procainamide) • Ticlopidine
Antimicrobial	• Trimethoprim-sulfamethoxazole • Quinine • Acyclovir

This patient has a sore throat, fever, and pharyngeal ulcers. Although this constellation of symptoms often occurs as a consequence of viral upper respiratory tract infection, the recent initiation of antithyroid medication for **Graves disease** should raise strong suspicion for **drug-induced neutropenia**.

Patients with Graves disease are often treated initially with thionamide medications such as **methimazole** or **propylthiouracil** (PTU) to achieve a euthyroid state prior to radioiodine therapy or surgery. However, these medications cause **severe neutropenia** (absolute neutrophil count <500/mm^3) in approximately 1 in 200 individuals. This side effect of therapy is thought to occur due to the interaction of the thionamide with reactive oxidative products (eg, myeloperoxidase, hydrogen peroxide), leading to generation of drug metabolites (eg, propyl thioester, sulfonic acid) that covalently attach to the neutrophil surface. Antibodies then form against these new antigens (haptens), resulting in antibody-dependent cellular cytotoxicity.

Drug-induced neutropenia most often presents with **oropharyngeal ulcers** and **fever** (ie, mucus membrane infection). Laboratory evaluation usually shows isolated leukopenia (eg, no anemia or thrombocytopenia).

https://t.me/USMLEWorldStep1

This patient has a sore throat, fever, and pharyngeal ulcers. Although this constellation of symptoms often occurs as a consequence of viral upper respiratory tract infection, the recent initiation of antithyroid medication for **Graves disease** should raise strong suspicion for **drug-induced neutropenia**.

Patients with Graves disease are often treated initially with thionamide medications such as **methimazole** or **propylthiouracil** (PTU) to achieve a euthyroid state prior to radioiodine therapy or surgery. However, these medications cause **severe neutropenia** (absolute neutrophil count <500/mm^3) in approximately 1 in 200 individuals. This side effect of therapy is thought to occur due to the interaction of the thionamide with reactive oxidative products (eg, myeloperoxidase, hydrogen peroxide), leading to generation of drug metabolites (eg, propyl thioester, sulfonic acid) that covalently attach to the neutrophil surface. Antibodies then form against these new antigens (haptens), resulting in antibody-dependent cellular cytotoxicity.

Drug-induced neutropenia most often presents with **oropharyngeal ulcers** and **fever** (ie, mucus membrane infection). Laboratory evaluation usually shows isolated leukopenia (eg, no anemia or thrombocytopenia). Because patients with drug-induced neutropenia are at risk for **severe infections**, the offending drug should be immediately **discontinued**. This usually resolves the neutropenia within 1-3 weeks.

(Choice A) Patients with autoimmune thyroid disease (eg, Graves disease) are at risk for other autoimmune endocrinopathies, including adrenal insufficiency. However, acute adrenal insufficiency typically presents with refractory hypotension, vomiting, abdominal pain, and weakness. Pharyngitis would be atypical.

(Choice C) Excessive suppression of thyroid function by antithyroid drugs can lead to a hypothyroid state, which can present with fatigue. However, patients with hypothyroidism demonstrate weight gain, not weight loss; other symptoms (eg, cold intolerance, hair and skin changes) are also usually present.

(Choice D) Undertreatment of this patient's hyperthyroidism could result in a residual hyperthyroid state (ie, thyroid hormone–induced severe hypermetabolism), which can present with fever, tachycardia, and dehydration. However, hypertension and tremor would likely be present; pharyngeal infection is unexpected.

(Choice E) Several viral infections (eg, HIV) can cause virus-induced lymphocyte destruction. Although the loss of lymphocytes from viral infection can lead to pharyngeal infection, the presence of fever and pharyngitis shortly after initiation of antithyroid medication is more suggestive of drug-induced neutropenia.

https://t.me/USMLEWorldStep1

individuals. This side effect of therapy is thought to occur due to the interaction of the thionamide with reactive oxidative products (eg, myeloperoxidase, hydrogen peroxide), leading to generation of drug metabolites (eg, propyl thioester, sulfonic acid) that covalently attach to the neutrophil surface. Antibodies then form against these new antigens (haptens), resulting in antibody-dependent cellular cytotoxicity.

Drug-induced neutropenia most often presents with **oropharyngeal ulcers** and **fever** (ie, mucus membrane infection). Laboratory evaluation usually shows isolated leukopenia (eg, no anemia or thrombocytopenia). Because patients with drug-induced neutropenia are at risk for **severe infections**, the offending drug should be immediately **discontinued**. This usually resolves the neutropenia within 1-3 weeks.

(Choice A) Patients with autoimmune thyroid disease (eg, Graves disease) are at risk for other autoimmune endocrinopathies, including adrenal insufficiency. However, acute adrenal insufficiency typically presents with refractory hypotension, vomiting, abdominal pain, and weakness. Pharyngitis would be atypical.

(Choice C) Excessive suppression of thyroid function by antithyroid drugs can lead to a hypothyroid state, which can present with fatigue. However, patients with hypothyroidism demonstrate weight gain, not weight loss; other symptoms (eg, cold intolerance, hair and skin changes) are also usually present.

(Choice D) Undertreatment of this patient's hyperthyroidism could result in a residual hyperthyroid state (ie, thyroid hormone–induced severe hypermetabolism), which can present with fever, tachycardia, and dehydration. However, hypertension and tremor would likely be present; pharyngeal infection is unexpected.

(Choice E) Several viral infections (eg, HIV) can cause virus-induced lymphocyte destruction. Although the loss of lymphocytes from viral infection can lead to pharyngeal infection, the presence of fever and pharyngitis shortly after initiation of antithyroid medication is more suggestive of drug-induced neutropenia.

Educational objective:
Drug-induced neutropenia is the major side effect of the first-line medications used to treat Graves disease. Initial manifestations usually include fever and oropharyngeal ulcers.

References

- Antithyroid drug-induced agranulocytosis: state of the art on diagnosis and management.

Pharmacology Endocrine, Diabetes & Metabolism Hyperthyroidism

https://t.me/USMLEWorldStep1

A newborn boy who was born at 39 weeks gestation by normal vaginal delivery has a serum TSH above the normal range and serum thyroxine (T4) below the normal range for his age. His mother has no medical conditions. On examination, the patient's length and weight are normal, and he has no apparent congenital malformations. Which of the following is the most likely cause of this patient's condition?

- A. Central hypothyroidism
- B. Generalized thyroid hormone resistance
- C. Reduced thyroid-binding globulin
- D. Thyroid dysgenesis
- E. TSH receptor–stimulating antibodies

Submit

https://t.me/USMLEWorldStep1

A newborn boy who was born at 39 weeks gestation by normal vaginal delivery has a serum TSH above the normal range and serum thyroxine (T4) below the normal range for his age. His mother has no medical conditions. On examination, the patient's length and weight are normal, and he has no apparent congenital malformations. Which of the following is the most likely cause of this patient's condition?

- A. Central hypothyroidism (9%)
- ✗ B. Generalized thyroid hormone resistance (11%)
- C. Reduced thyroid-binding globulin (17%)
- ✓ D. Thyroid dysgenesis (56%)
- E. TSH receptor–stimulating antibodies (4%)

Incorrect
Correct answer
D

56%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

Congenital hypothyroidism		
Cause	**Free & total T4**	**TSH**
• Primary hypothyroidism ◦ Thyroid dysgenesis ◦ TSH resistance	↓	↑
• Thyroid hormone resistance	↑	↑
• Central hypothyroidism	↓	↓
• Transient due to maternal exposure		

https://t.me/USMLEWorldStep1

Congenital hypothyroidism		
Cause	**Free & total T4**	**TSH**
• Primary hypothyroidism ◦ Thyroid dysgenesis ◦ TSH resistance	↓	↑
• Thyroid hormone resistance	↑	↑
• Central hypothyroidism	↓	↓
• Transient due to maternal exposure ◦ Iodine excess or deficiency ◦ TSH receptor–blocking antibodies ◦ Antithyroid medications	↓	↑
T4 = thyroxine.		

This patient has **primary hypothyroidism**, a congenital condition most commonly caused by **thyroid dysgenesis**. Thyroid dysgenesis refers to an underdeveloped thyroid (ie, **hypoplasia**, **aplasia**) or an ectopic thyroid, which can lie anywhere along the normal path of embryologic descent from the base of the tongue to its normal location anterior to the thyroid cartilage. Most cases are sporadic and isolated without other congenital abnormalities.

Newborns are usually asymptomatic due to the transplacental transfer of maternal thyroxine (T4), although levels are decreased compared to those of healthy patients. Because of insufficient feedback inhibition from **low T4** levels, **TSH** is **elevated**. Newborn screening allows for early identification and treatment with levothyroxine, which prevents the development of neurocognitive dysfunction.

(Choice A) Hypothalamic or pituitary dysfunction can lead to central hypothyroidism due to deficient TSH production. TSH and T4 levels would both be low.

https://t.me/USMLEWorldStep1

This patient has **primary hypothyroidism**, a congenital condition most commonly caused by **thyroid dysgenesis**. Thyroid dysgenesis refers to an underdeveloped thyroid (ie, **hypoplasia**, **aplasia**) or an ectopic thyroid, which can lie anywhere along the normal path of embryologic descent from the base of the tongue to its normal location anterior to the thyroid cartilage. Most cases are sporadic and isolated without other congenital abnormalities.

Newborns are usually asymptomatic due to the transplacental transfer of maternal thyroxine (T4), although levels are decreased compared to those of healthy patients. Because of insufficient feedback inhibition from **low T4** levels, **TSH** is **elevated**. Newborn screening allows for early identification and treatment with levothyroxine, which prevents the development of neurocognitive dysfunction.

(Choice A) Hypothalamic or pituitary dysfunction can lead to central hypothyroidism due to deficient TSH production. TSH and T4 levels would both be low.

(Choice B) Congenital hypothyroidism can also be caused by thyroid hormone resistance (eg, thyroid hormone receptor mutations). However, TSH and T4 levels would be elevated due to impaired thyroid hormone feedback.

(Choice C) Thyroid-binding globulin (TBG) is a transport protein that binds T4. TBG deficiency results in a euthyroid state characterized by a low level of total T4 but normal TSH and free T4 levels.

(Choice E) Neonatal Graves disease is characterized by the transplacental transfer of maternal TSH receptor–stimulating antibodies due to maternal Graves disease. This condition causes transient hyperthyroidism with elevated T4 and decreased TSH.

Educational objective:
Thyroid dysgenesis (ie, hypoplasia, aplasia, ectopy) is the most common cause of primary congenital hypothyroidism. In this condition, TSH is elevated and thyroxine (T4) is low.

References

- Congenital hypothyroidism.

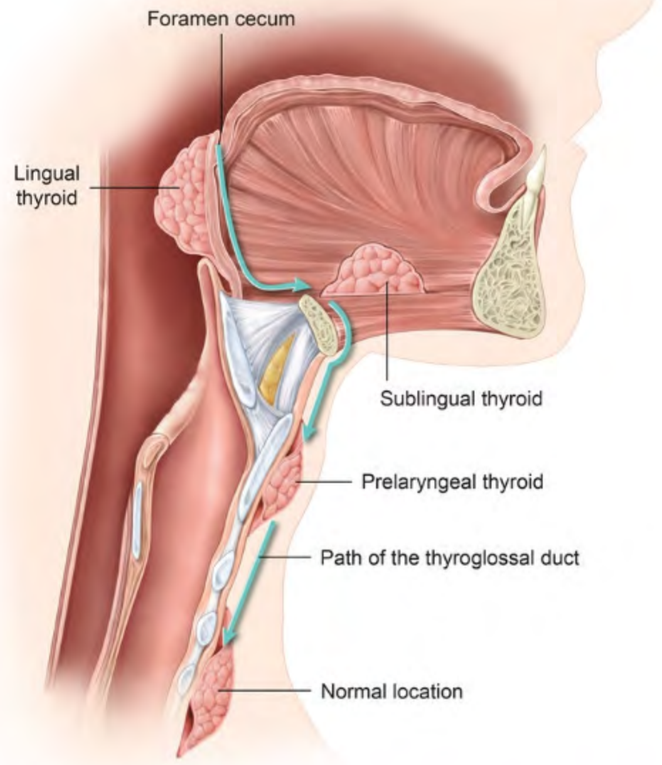
Pathophysiology	Endocrine, Diabetes & Metabolism	Hypothyroidism
Subject	System	Topic

https://t.me/USMLEWorldStep1

- Transient due to maternal exposure

Exhibit Display

Thyroid migration



©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

This p
dysge
thyroi
norma
abnor

Newb
are de
levels,
prever

(Choi
produc

(Choi
recept

(Choi
euthyr

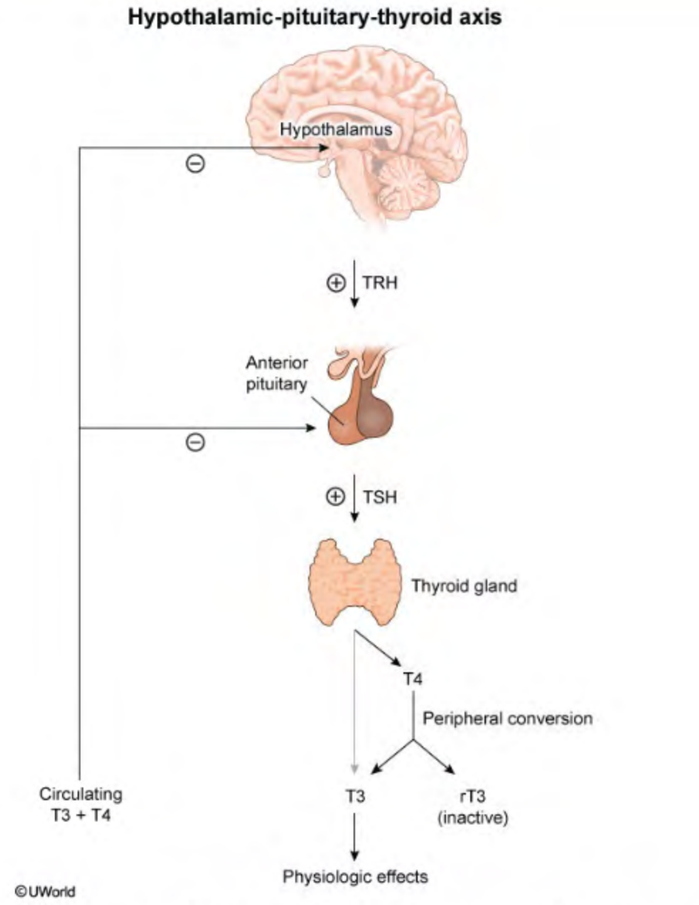
(Choi
stimul
elevat

Educational objective:
Thyroid dysgenesis (ie, hypoplasia, aplasia, ectopy) is the most common cause of primary congenital

https://t.me/USMLEWorldStep1

- Transient due to maternal exposure

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

This p
dysge
thyroi
norma
abnor

Newb
are de
levels,
prever

(Choi
produ

(Choi
recept

(Choi
euthyr

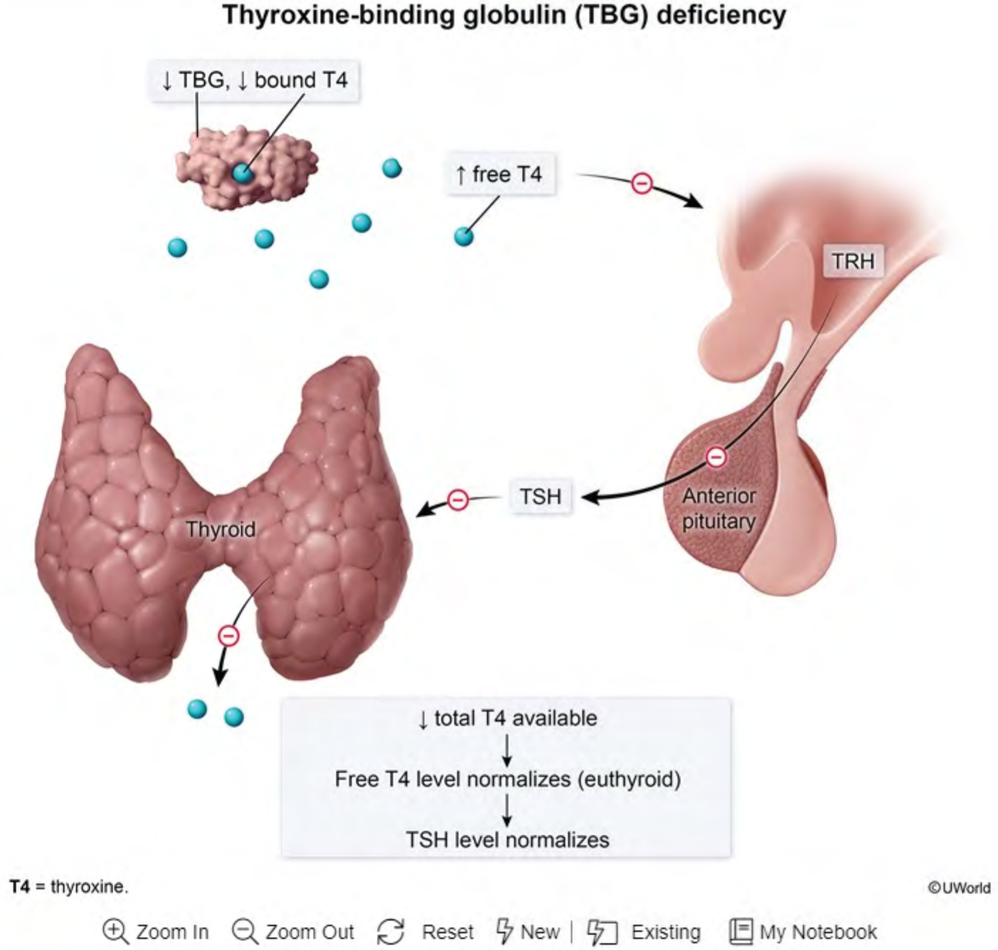
(Choi
stimul
elevat

Educational objective:
Thyroid dysgenesis (ie, hypoplasia, aplasia, ectopy) is the most common cause of primary congenital

https://t.me/USMLEWorldStep1

• Transient due to maternal exposure		

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

This p
dysge
thyroi
norma
abnor

Newb
are de
levels,
prever

(Choi
produ

(Choi
recept

(Choi
euthyr

(Choi
stimul
elevat

Educational objective:
Thyroid dysgenesis (ie, hypoplasia, aplasia, ectopy) is the most common cause of primary congenital

https://t.me/USMLEWorldStep1

A 65-year-old woman comes to the emergency department due to left leg pain and swelling for the past day. She has had no trauma or fever. The patient has a history of hypertension, congestive heart failure, type 2 diabetes mellitus, and osteoporosis. Family history is notable for breast cancer in her mother and sister. She takes multiple medications. Temperature is 37.8 C (100 F), blood pressure is 130/80 mm Hg, and pulse is 99/min. Pulse oximetry shows 98% on ambient air. The lungs are clear to auscultation, and heart sounds are normal without murmur. There is tenderness and edema of the left lower extremity up to the mid thigh. Venous Doppler ultrasonography reveals an occluding thrombus in the left femoral and popliteal veins. Which of the following pharmacotherapies most likely contributed to this patient's current condition?

- A. Alendronate
- B. Chlorthalidone
- C. Empagliflozin
- D. Liraglutide
- E. Raloxifene
- F. Sacubitril-valsartan
- G. Spironolactone

Submit

https://t.me/USMLEWorldStep1

A 65-year-old woman comes to the emergency department due to left leg pain and swelling for the past day. She has had no trauma or fever. The patient has a history of hypertension, congestive heart failure, type 2 diabetes mellitus, and osteoporosis. Family history is notable for breast cancer in her mother and sister. She takes multiple medications. Temperature is 37.8 C (100 F), blood pressure is 130/80 mm Hg, and pulse is 99/min. Pulse oximetry shows 98% on ambient air. The lungs are clear to auscultation, and heart sounds are normal without murmur. There is tenderness and edema of the left lower extremity up to the mid thigh. Venous Doppler ultrasonography reveals an occluding thrombus in the left femoral and popliteal veins. Which of the following pharmacotherapies most likely contributed to this patient's current condition?

- A. Alendronate (7%)
- ✗ B. Chlorthalidone (6%)
- C. Empagliflozin (2%)
- D. Liraglutide (2%)
- ✓ E. Raloxifene (72%)
- F. Sacubitril-valsartan (3%)
- G. Spironolactone (4%)

Incorrect
Correct answer
E

72%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

Selective estrogen receptor modulators	
Drugs	• Tamoxifen • Raloxifene

https://t.me/USMLEWorldStep1

Selective estrogen receptor modulators	
Drugs	• Tamoxifen • Raloxifene
Mechanism of action	• Competitive inhibitor of estrogen binding • Mixed agonist/antagonist action
Indications	• Prevention of breast cancer in high-risk patients • Tamoxifen: adjuvant treatment of breast cancer • Raloxifene: postmenopausal osteoporosis
Adverse effects	• Hot flashes • Venous thromboembolism • Endometrial hyperplasia & carcinoma (tamoxifen only) • Uterine sarcoma (tamoxifen only)

Selective estrogen receptor modulators (SERMs), such as raloxifene and tamoxifen, are nonsteroidal compounds that bind to estrogen receptors and exhibit estrogen antagonist and agonist properties in a tissue-specific manner. **Raloxifene** has estrogen agonist activity on bone, inhibiting bone resorption and improving bone mineral density while exhibiting estrogen antagonist activity in the breast and endometrial tissue.

Medicines with estrogen agonist activity, including SERMs, oral contraceptives, and hormone replacement therapy, cause a prothrombotic state and can increase the risk for **venous thromboembolism** (VTE). Proposed mechanisms include increased levels of clotting factors (eg, prothrombin; fibrinogen; factor VII, VIII, X) and activated protein C resistance. Current or prior thromboembolic disorders are contraindications to SERM use.

(Choice A) Bisphosphonates (eg, alendronate) inhibit osteoclast-mediated bone resorption. Side effects include hypocalcemia, esophagitis, and osteonecrosis of the jaw. Bisphosphonates have no estrogenic activity and do not increase the risk for VTE.

(Choice B) Thiazide diuretics (eg, chlorthalidone) inhibit Na^+/Cl^- cotransporters in the distal convoluted tubule.

https://t.me/USMLEWorldStep1

Selective estrogen receptor modulators (SERMs), such as raloxifene and tamoxifen, are nonsteroidal compounds that bind to estrogen receptors and exhibit estrogen antagonist and agonist properties in a tissue-specific manner. **Raloxifene** has estrogen agonist activity on bone, inhibiting bone resorption and improving bone mineral density while exhibiting estrogen antagonist activity in the breast and endometrial tissue.

Medicines with estrogen agonist activity, including SERMs, oral contraceptives, and hormone replacement therapy, cause a prothrombotic state and can increase the risk for **venous thromboembolism** (VTE). Proposed mechanisms include increased levels of clotting factors (eg, prothrombin; fibrinogen; factor VII, VIII, X) and activated protein C resistance. Current or prior thromboembolic disorders are contraindications to SERM use.

(Choice A) Bisphosphonates (eg, alendronate) inhibit osteoclast-mediated bone resorption. Side effects include hypocalcemia, esophagitis, and osteonecrosis of the jaw. Bisphosphonates have no estrogenic activity and do not increase the risk for VTE.

(Choice B) Thiazide diuretics (eg, chlorthalidone) inhibit Na^+/Cl^- cotransporters in the distal convoluted tubule, decreasing reabsorption of Na^+ and increasing reabsorption of calcium, which can be beneficial in patients with osteoporosis. Side effects include electrolyte abnormalities, hyperglycemia, and hyperlipidemia.

(Choice C) Sodium-glucose cotransporter 2 inhibitors (eg, empagliflozin) reduce reabsorption of glucose in the proximal renal tubule, leading to urinary glucose excretion. Side effects include urinary tract and genital mycotic infections as well as hypotension.

(Choice D) Glucagon-like peptide-1 (GLP-1) is released by the small intestine in response to food and induces glucose-dependent insulin release from pancreatic beta cells. GLP-1 agonists (eg, liraglutide) lower blood glucose with little hypoglycemia risk, but can cause gastrointestinal upset and weight loss.

(Choice F) Sacubitril is a neprilysin inhibitor that increases atrial natriuretic peptide and brain natriuretic peptide levels (thereby promoting diuresis and vasodilation) in patients with heart failure. It is administered with an angiotensin II receptor blocker (valsartan) to offset the associated increase in angiotensin II levels. Side effects include cough, hyperkalemia, and renal impairment.

(Choice G) Spironolactone is an aldosterone antagonist used in patients with heart failure. It has prominent anti-androgenic effects, which can lead to gynecomastia in male patients due to unopposed estrogenic effects on

https://t.me/USMLEWorldStep1

cause a prothrombotic state and can increase the risk for **venous thromboembolism** (VTE). Proposed mechanisms include increased levels of clotting factors (eg, prothrombin; fibrinogen; factor VII, VIII, X) and activated protein C resistance. Current or prior thromboembolic disorders are contraindications to SERM use.

(Choice A) Bisphosphonates (eg, alendronate) inhibit osteoclast-mediated bone resorption. Side effects include hypocalcemia, esophagitis, and osteonecrosis of the jaw. Bisphosphonates have no estrogenic activity and do not increase the risk for VTE.

(Choice B) Thiazide diuretics (eg, chlorthalidone) inhibit Na^+/Cl^- cotransporters in the distal convoluted tubule, decreasing reabsorption of Na^+ and increasing reabsorption of calcium, which can be beneficial in patients with osteoporosis. Side effects include electrolyte abnormalities, hyperglycemia, and hyperlipidemia.

(Choice C) Sodium-glucose cotransporter 2 inhibitors (eg, empagliflozin) reduce reabsorption of glucose in the proximal renal tubule, leading to urinary glucose excretion. Side effects include urinary tract and genital mycotic infections as well as hypotension.

(Choice D) Glucagon-like peptide-1 (GLP-1) is released by the small intestine in response to food and induces glucose-dependent insulin release from pancreatic beta cells. GLP-1 agonists (eg, liraglutide) lower blood glucose with little hypoglycemia risk, but can cause gastrointestinal upset and weight loss.

(Choice F) Sacubitril is a neprilysin inhibitor that increases atrial natriuretic peptide and brain natriuretic peptide levels (thereby promoting diuresis and vasodilation) in patients with heart failure. It is administered with an angiotensin II receptor blocker (valsartan) to offset the associated increase in angiotensin II levels. Side effects include cough, hyperkalemia, and renal impairment.

(Choice G) Spironolactone is an aldosterone antagonist used in patients with heart failure. It has prominent anti-androgenic effects, which can lead to gynecomastia in male patients due to unopposed estrogenic effects on breast tissue. However, it has minimal effects on estrogen levels and does not increase the risk of VTE.

Educational objective:
Raloxifene is a selective estrogen receptor modulator (SERM) that has estrogen agonist activity on bone and decreases bone resorption. Medicines with estrogen agonist activity, including SERMs, oral contraceptives, and hormone replacement therapy, can increase the risk for venous thromboembolism.

https://t.me/USMLEWorldStep1

A 1-week-old boy is brought to the emergency department with poor feeding, lethargy, and unusual "muscle movements" involving the left thumb and hand over the last 2 days. The patient's mother had appropriate prenatal care, a normal pregnancy, and took no medications other than prenatal vitamins. The infant's vital signs are normal, but unusual flexion of the left wrist and thumb and extension of the fingers are observed with cuff blood pressure measurement. Physical examination reveals a hypoplastic mandible, low-set ears, bifid uvula, and cleft palate. A chest x-ray reveals decreased soft-tissue attenuation in the right anterior mediastinum. These findings most likely suggest impaired development of which of the following embryonic structures?

- A. Anterior neuropore
- B. Foramen cecum
- C. Rathke pouch
- D. Second pharyngeal cleft
- E. Third pharyngeal pouch

Submit

https://t.me/USMLEWorldStep1

A 1-week-old boy is brought to the emergency department with poor feeding, lethargy, and unusual "muscle movements" involving the left thumb and hand over the last 2 days. The patient's mother had appropriate prenatal care, a normal pregnancy, and took no medications other than prenatal vitamins. The infant's vital signs are normal, but unusual flexion of the left wrist and thumb and extension of the fingers are observed with cuff blood pressure measurement. Physical examination reveals a hypoplastic mandible, low-set ears, bifid uvula, and cleft palate. A chest x-ray reveals decreased soft-tissue attenuation in the right anterior mediastinum. These findings most likely suggest impaired development of which of the following embryonic structures?

- ✗ A. Anterior neuropore (3%)
- B. Foramen cecum (1%)
- C. Rathke pouch (5%)
- D. Second pharyngeal cleft (12%)
- ✓ E. Third pharyngeal pouch (77%)

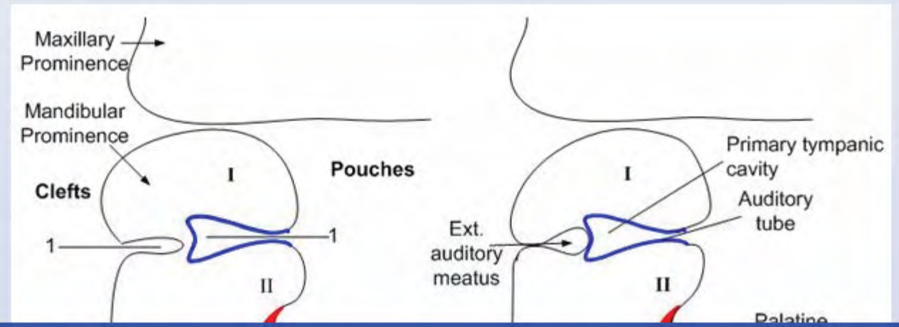
Incorrect
Correct answer
E

77%
Answered correctly

04 secs
Time Spent

2023
Version

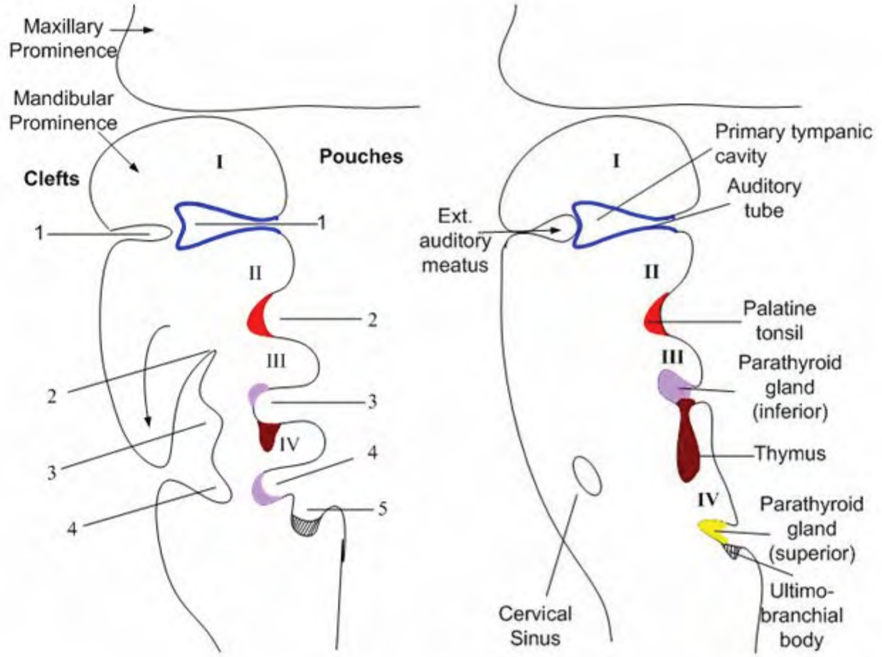
Explanation



https://t.me/USMLEWorldStep1

A 1-week-old boy is brought to the emergency department with poor feeding, lethargy, and unusual "muscle
mover
care, a
norma
pressu
palate
most li

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

A **22q11.2 microdeletion** underlies the spectrum of physical features seen in DiGeorge syndrome (DGS). Embryologically, the neural crest fails to migrate into the derivatives of the **third** (affects inferior **parathyroid** and thymus) and fourth (affects superior parathyroid) pharyngeal/branchial pouches. The consequent parathyroid and thymic hypoplasia results in **hypocalcemia** and T cell deficiency, respectively.

The hypocalcemia in DGS leads to increased neuromuscular excitability, which manifests as tetany, carpopedal spasms, or seizures. Tapping on the facial nerve usually elicits **twitching of the nose and lips (Chvostek sign)**, and inflation of the blood pressure cuff leads to **carpal spasm (Trousseau sign)**. Normally, the thymic shadow is visible on a newborn's x-ray. Its absence reflects thymic hypoplasia, which leads to T cell dysfunction and results in recurrent viral, fungal, and protozoan infections.

Conotruncal cardiac anomalies (eg, interrupted aortic arch, truncus arteriosus) may also result from failure of neural crest migration. If there is additional involvement of the first and second pharyngeal/branchial pouches, patients with DGS may have features such as hypertelorism, short palpebral fissures, micrognathia, bifid uvula, and cleft palate.

(Choice A) Failure of the anterior neuropore to close leads to neural tube defects such as anencephaly. Neural tube defects can be prevented with maternal folic acid supplementation.

(Choice B) The foramen cecum is a depression on the tongue that represents the embryological remnant of the superior end of the obliterated thyroglossal duct. A persistent duct results in a thyroglossal cyst that presents as a midline neck mass.

(Choice C) Rathke pouch represents an invaginated oral ectoderm that eventually develops into the anterior pituitary. Craniopharyngiomas arise from remnants of this pouch and can result in hypopituitarism, hydrocephalus, and diabetes insipidus, but not hypocalcemia.

(Choice D) The second branchial cleft (ie, second pharyngeal groove) is normally obliterated in utero. Persistence leads to a branchial cleft cyst between the angle of the mandible and sternocleidomastoid muscle.

Educational objective:
DiGeorge syndrome results from maldevelopment of the third (inferior parathyroid and thymus) and fourth (superior parathyroid) pharyngeal/branchial pouches. Subsequent parathyroid and thymic hypoplasia results in

https://t.me/USMLEWorldStep1

thymic hypoplasia results in **hypocalcemia** and T cell deficiency, respectively.

The hypocalcemia in DGS leads to increased neuromuscular excitability, which manifests as tetany, carpopedal spasms, or seizures. Tapping on the facial nerve usually elicits **twitching of the nose and lips (Chvostek sign)**, and inflation of the blood pressure cuff leads to **carpal spasm (Trousseau sign)**. Normally, the thymic shadow is visible on a newborn's x-ray. Its absence reflects thymic hypoplasia, which leads to T cell dysfunction and results in recurrent viral, fungal, and protozoan infections.

Conotruncal cardiac anomalies (eg, interrupted aortic arch, truncus arteriosus) may also result from failure of neural crest migration. If there is additional involvement of the first and second pharyngeal/branchial pouches, patients with DGS may have features such as hypertelorism, short palpebral fissures, micrognathia, bifid uvula, and cleft palate.

(Choice A) Failure of the anterior neuropore to close leads to neural tube defects such as anencephaly. Neural tube defects can be prevented with maternal folic acid supplementation.

(Choice B) The foramen cecum is a depression on the tongue that represents the embryological remnant of the superior end of the obliterated thyroglossal duct. A persistent duct results in a thyroglossal cyst that presents as a midline neck mass.

(Choice C) Rathke pouch represents an invaginated oral ectoderm that eventually develops into the anterior pituitary. Craniopharyngiomas arise from remnants of this pouch and can result in hypopituitarism, hydrocephalus, and diabetes insipidus, but not hypocalcemia.

(Choice D) The second branchial cleft (ie, second pharyngeal groove) is normally obliterated in utero. Persistence leads to a branchial cleft cyst between the angle of the mandible and sternocleidomastoid muscle.

Educational objective:
DiGeorge syndrome results from maldevelopment of the third (inferior parathyroid and thymus) and fourth (superior parathyroid) pharyngeal/branchial pouches. Subsequent parathyroid and thymic hypoplasia results in hypocalcemia and T cell deficiency.

References

- Velocardiofacial syndrome, DiGeorge syndrome: the chromosome 22q11.2 deletion syndromes.

https://t.me/USMLEWorldStep1

4

gland
(superior)

Exhibit Display

Thymus x-ray | Thymus x-ray



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

A **22q**
Embry
thymu
thymic

The hy
spasm
and in
visible
in recu

Conot
neural
patien
and cl

(Choi
tube d

(Choi
superi
midlin

(Choi
pituita
and di

(Choice D) The second branchial cleft (ie, second pharyngeal groove) is normally obliterated in utero. Persistence leads to a branchial cleft cyst between the angle of the mandible and sternocleidomastoid muscle.

https://t.me/USMLEWorldStep1

thymic hypoplasia results in **hypocalcemia** and T cell deficiency, respectively.

The hy
spasm
and in
visible
in recu

Conot
neural
patien
and cl

(Choi
tube d

(Choi
superi
midlin

(Choi
pituita
and di

(Choi
Persis

Educa
DiGeo
parath
hypoca

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

References

- Velocardiofacial syndrome, DiGeorge syndrome: the chromosome 22q11.2 deletion syndromes.

https://t.me/USMLEWorldStep1

thymic hypoplasia results in **hypocalcemia** and T cell deficiency, respectively.

The hy
spasm
and in
visible
in recu

Conot
neural
patien
and cl

(Choi
tube d

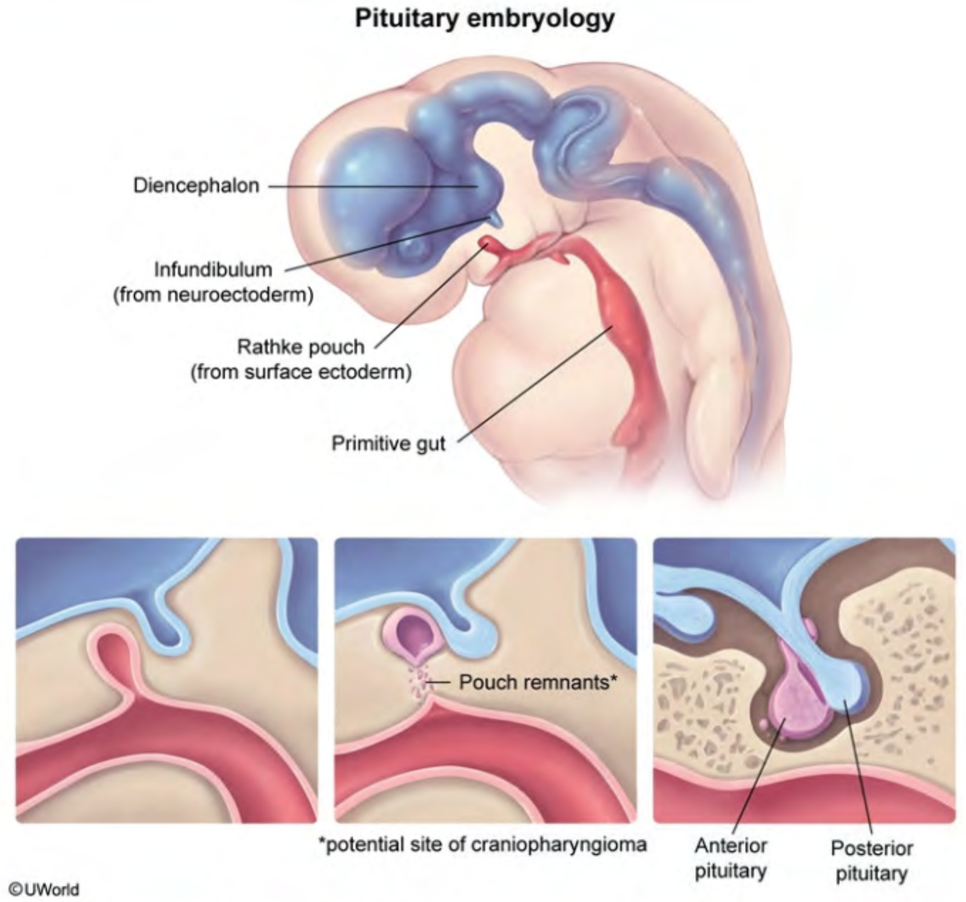
(Choi
superi
midlin

(Choi
pituita
and di

(Choi
Persis

Educa
DiGeo
parath
hypoc

Exhibit Display



Zoom In Zoom Out Reset New | Existing My Notebook

References

- Velocardiofacial syndrome, DiGeorge syndrome: the chromosome 22q11.2 deletion syndromes.

https://t.me/USMLEWorldStep1

A group of investigators is studying the regulation of catecholamine synthesis in response to severe stress. In the experiments, subject rats are randomly assigned to either an experimental or a control group. The experimental rats undergo resection of the pituitary gland, and the control rats undergo craniotomy without pituitary resection. The experimental animals are subsequently found to have decreased production of epinephrine by the adrenal medulla and cortisol from the adrenal cortex compared with the control animals. Decreased activity of which of the following enzymes is most likely responsible for the lower epinephrine in the experimental animals?

- A. Catechol-O-methyl transferase
- B. Dopa decarboxylase
- C. Dopamine beta-hydroxylase
- D. Monoamine oxidase
- E. Phenylalanine hydroxylase
- F. Phenylethanolamine-N-methyltransferase
- G. Tyrosine hydroxylase

Submit

https://t.me/USMLEWorldStep1

A group of investigators is studying the regulation of catecholamine synthesis in response to severe stress. In the experiments, subject rats are randomly assigned to either an experimental or a control group. The experimental rats undergo resection of the pituitary gland, and the control rats undergo craniotomy without pituitary resection. The experimental animals are subsequently found to have decreased production of epinephrine by the adrenal medulla and cortisol from the adrenal cortex compared with the control animals. Decreased activity of which of the following enzymes is most likely responsible for the lower epinephrine in the experimental animals?

- A. Catechol-O-methyl transferase (13%)
- ✕ B. Dopa decarboxylase (11%)
- C. Dopamine beta-hydroxylase (16%)
- D. Monoamine oxidase (4%)
- E. Phenylalanine hydroxylase (3%)
- ✓ F. Phenylethanolamine-N-methyltransferase (41%)
- G. Tyrosine hydroxylase (10%)

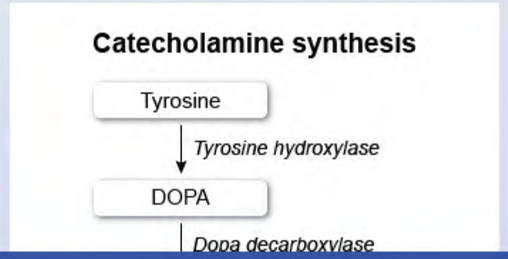
Incorrect
Correct answer
F

41%
Answered correctly

12 mins, 31 secs
Time Spent

2023
Version

Explanation

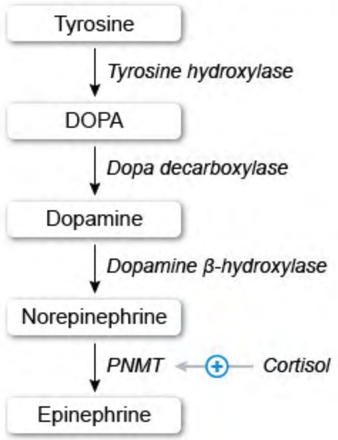


https://t.me/USMLEWorldStep1

F. Phenylethanolamine-N-methyltransferase (41%)

Exhibit Display

Catecholamine synthesis

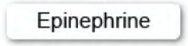


PNMT = phenylethanolamine-N-methyltransferase. ©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

The 3
dopam
predor
conver
the synthesis of catecholamines. DOPA is converted to dopamine by dopa decarboxylase **(Choice B)**, which is then converted to norepinephrine by dopamine beta-hydroxylase **(Choice C)**. In the adrenal medulla,

https://t.me/USMLEWorldStep1



PNMT = phenylethanolamine-N-methyltransferase. ©UWorld

The 3 main circulating catecholamines are dopamine, norepinephrine, and epinephrine. Norepinephrine and dopamine are produced in the central as well as the peripheral nervous system, whereas epinephrine is predominantly produced in the **adrenal medulla**. The first step in the synthesis of catecholamines is the conversion of tyrosine to dihydroxyphenylalanine (DOPA) by tyrosine hydroxylase. This is the rate-limiting step in the synthesis of catecholamines. DOPA is converted to dopamine by dopa decarboxylase **(Choice B)**, which is then converted to norepinephrine by dopamine beta-hydroxylase **(Choice C)**. In the adrenal medulla, norepinephrine is rapidly converted to epinephrine by **phenylethanolamine-N-methyltransferase** (PNMT).

Expression of PNMT in the adrenal medulla is upregulated by cortisol. Because the venous drainage of the adrenal cortex passes through the adrenal medulla, cortisol concentrations in the medulla can be very high, and PNMT is expressed at a high level. However, following **pituitary resection**, the loss of ACTH leads to decreased synthesis of cortisol in the adrenal cortex. The result is **decreased PNMT activity** and reduced conversion of norepinephrine to epinephrine.

(Choices A and D) Catechol-O-methyltransferase (COMT) and monoamine oxidase (MAO) are responsible for inactivation of catecholamines. COMT converts epinephrine to metanephrine and norepinephrine to normetanephrine; MAO converts metanephrine and normetanephrine to vanillylmandelic acid.

(Choices E and G) Tyrosine required for the synthesis of catecholamines is obtained from either dietary intake or by conversion of phenylalanine by phenylalanine hydroxylase in the liver. Deficiency of phenylalanine hydroxylase enzyme causes phenylketonuria. Tyrosine hydroxylase deficiency impairs catecholamine synthesis and causes infantile parkinsonism and progressive encephalopathy.

Educational objective:
Cortisol increases the conversion of norepinephrine to epinephrine in the adrenal medulla by increasing the expression of phenylethanolamine-N-methyltransferase.

References

- Stress-triggered changes in peripheral catecholaminergic systems.

https://t.me/USMLEWorldStep1

A 45-year-old woman calls 911 due to severe chest pain and dyspnea. The emergency medical team finds the patient unresponsive with no pulse, and she does not revive despite extensive cardiopulmonary resuscitation efforts. She had a prolonged history of systemic lupus erythematosus treated with multiple medications and was recently evaluated for progressive muscle weakness. Records from the patient's most recent office visit show an elevated blood pressure and examination findings of facial plethora, truncal obesity, and skin ecchymoses. She was also found to have mild hyperglycemia. Medical history included a left hip replacement for osteonecrosis of the femoral head 1 year ago. At autopsy, she is found to have an occluding thrombus in the left main coronary artery, which likely led to sudden cardiac death. Examination of this patient's adrenal glands is most likely to reveal which of the following findings?

- A. Adrenocortical adenoma
- B. Bilateral cortical atrophy
- C. Diffuse cortical hyperplasia
- D. Diffuse cortical hypertrophy
- E. Nodular cortical hyperplasia

Submit

https://t.me/USMLEWorldStep1

A 45-year-old woman calls 911 due to severe chest pain and dyspnea. The emergency medical team finds the patient unresponsive with no pulse, and she does not revive despite extensive cardiopulmonary resuscitation efforts. She had a prolonged history of systemic lupus erythematosus treated with multiple medications and was recently evaluated for progressive muscle weakness. Records from the patient's most recent office visit show an elevated blood pressure and examination findings of facial plethora, truncal obesity, and skin ecchymoses. She was also found to have mild hyperglycemia. Medical history included a left hip replacement for osteonecrosis of the femoral head 1 year ago. At autopsy, she is found to have an occluding thrombus in the left main coronary artery, which likely led to sudden cardiac death. Examination of this patient's adrenal glands is most likely to reveal which of the following findings?

- ✗ A. Adrenocortical adenoma (8%)
- ✓ B. Bilateral cortical atrophy (66%)
- C. Diffuse cortical hyperplasia (15%)
- D. Diffuse cortical hypertrophy (7%)
- E. Nodular cortical hyperplasia (1%)

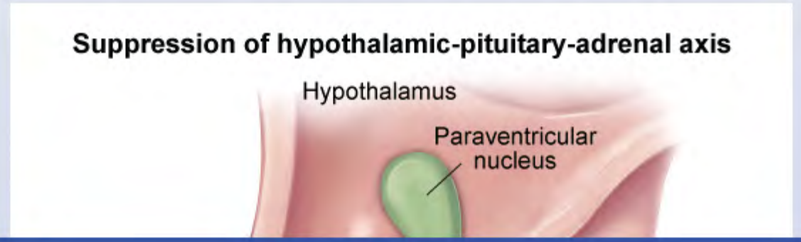
Incorrect
Correct answer
B

66%
Answered correctly

04 secs
Time Spent

2023
Version

Explanation



https://t.me/USMLEWorldStep1

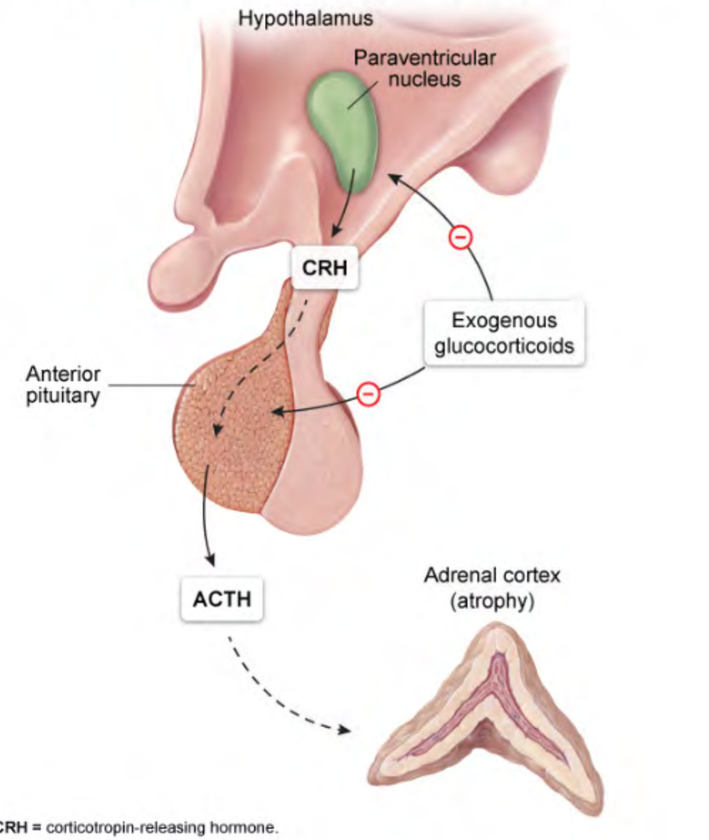
A 45-year-old woman calls 911 due to severe chest pain and dyspnea. The emergency medical team finds the patien
efforts
recent
elevat
was al
the fer
artery,
which

Incc
Corre
B

Expl

Exhibit Display

Suppression of hypothalamic-pituitary-adrenal axis



CRH = corticotropin-releasing hormone.

©UWorld

Zoom In Zoom Out Reset New | Existing My Notebook

https://t.me/USMLEWorldStep1

CRH = corticotropin-releasing hormone.
©UWorld

This patient has features of hypercortisolism, including hypertension, central obesity, muscular weakness, ecchymoses, and hyperglycemia. She most likely developed **iatrogenic Cushing syndrome** due to prolonged administration of glucocorticoids for management of systemic lupus erythematosus (SLE). **Chronic glucocorticoid use** can also cause osteonecrosis, and both Cushing syndrome and SLE itself can increase the risk for atherosclerosis and acute coronary events (as in this patient).

Exogenous glucocorticoid use **inhibits the entire hypothalamic-pituitary-adrenal axis**, leading to low levels of corticotropin-releasing hormone (CRH), ACTH, and endogenous cortisol. ACTH exerts a potent trophic (ie, growth promoting) effect on the adrenal zona fasciculata and reticularis; **long-term** suppression leads to **adrenocortical atrophy** (the zona glomerulosa is spared as angiotensin II is its primary trophic hormone). **Sudden cessation** of glucocorticoids after prolonged use can precipitate adrenocortical insufficiency and **adrenal crisis**.

(Choice A) Endogenous Cushing syndrome can be caused by an autonomous cortisol-producing adrenal tumor. However, this patient's history is more suggestive of exogenous glucocorticoid use.

(Choices C, D, and E) Bilateral cortical hyperplasia and hypertrophy occurs in patients with ACTH excess (eg, pituitary corticotroph adenoma [Cushing disease]). Varying degrees of adrenocortical nodularity can also be seen. However, this patient was likely taking exogenous glucocorticoids, which would suppress ACTH release and lead to adrenocortical atrophy.

Educational objective:
Long-term use of supraphysiologic doses of glucocorticoids causes suppression of the hypothalamic-pituitary-adrenal axis, which in turn leads to bilateral adrenocortical atrophy involving the zona fasciculata and reticularis. Sudden cessation of the exogenous corticosteroids can precipitate adrenal crisis.

References

- Management issues with exogenous steroid therapy.

Pathophysiology	Endocrine, Diabetes & Metabolism	Cushing syndrome
Subject	System	Topic

Copyright © UWorld. All rights reserved.

https://t.me/USMLEWorldStep1

CRH = corticotropin-releasing hormone.
©UWorld

This p
ecchy
admin
gluco
risk fo

Exoge
cortic
promo
atroph
glucoc

(Choi
Howev

(Choi
pituita
Howev
to adre

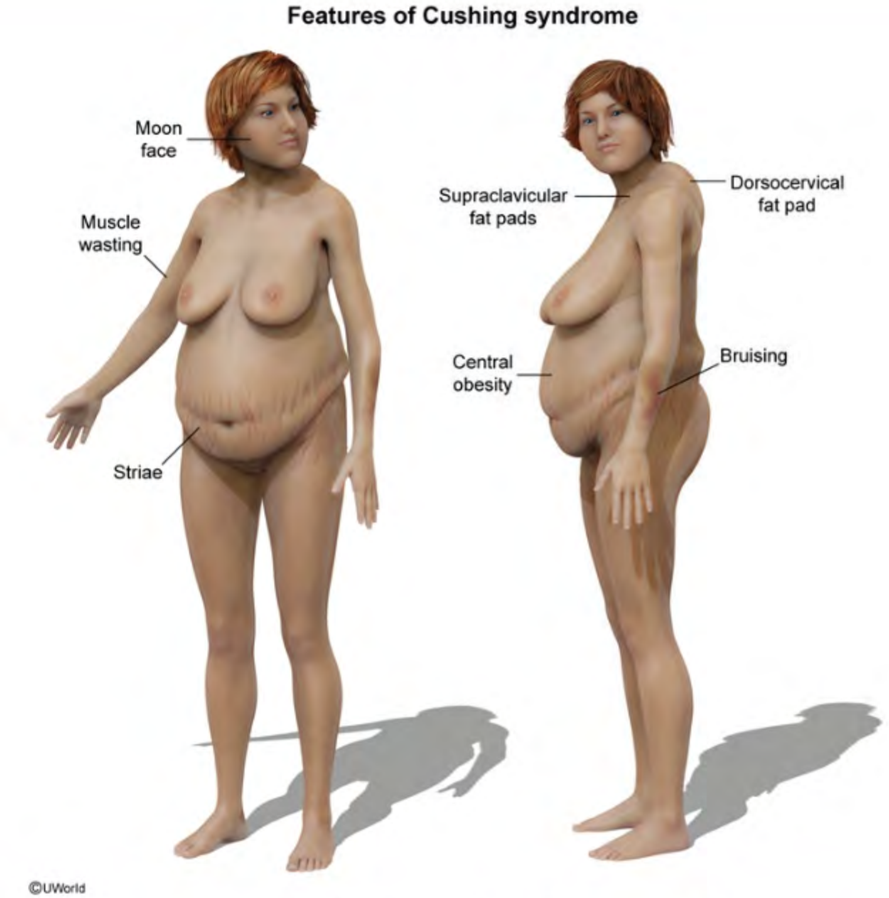
Educa
Long-t
adrena
Sudde

Refere
- Ma

Pathoph
Subject System Topic

Copyright © UWorld. All rights reserved.

Exhibit Display



Zoom In Zoom Out Reset New | Existing My Notebook

https://t.me/USMLEWorldStep1

A 22-year-old woman with no prenatal care has a normal vaginal delivery. On physical examination, the infant's external genitalia are atypical and ambiguous. There is an intermediate clitorophallic length and a perineal urethral opening. Well-circumscribed, mobile masses are palpable bilaterally in the inguinal area. Vital signs are normal. Serum testosterone level is within normal limits. A karyotype is performed and shows 46,XY. This infant most likely has a deficiency in which of the following enzymes?

- A. 5α-reductase
- B. 17-hydroxylase
- C. 21-hydroxylase
- D. Aromatase
- E. DHEA sulfatase

Submit

https://t.me/USMLEWorldStep1

A 22-year-old woman with no prenatal care has a normal vaginal delivery. On physical examination, the infant's external genitalia are atypical and ambiguous. There is an intermediate clitorophallic length and a perineal urethral opening. Well-circumscribed, mobile masses are palpable bilaterally in the inguinal area. Vital signs are normal. Serum testosterone level is within normal limits. A karyotype is performed and shows 46,XY. This infant most likely has a deficiency in which of the following enzymes?

- ✓ A. 5α-reductase (56%)
- B. 17-hydroxylase (20%)
- C. 21-hydroxylase (13%)
- D. Aromatase (5%)
- E. DHEA sulfatase (4%)

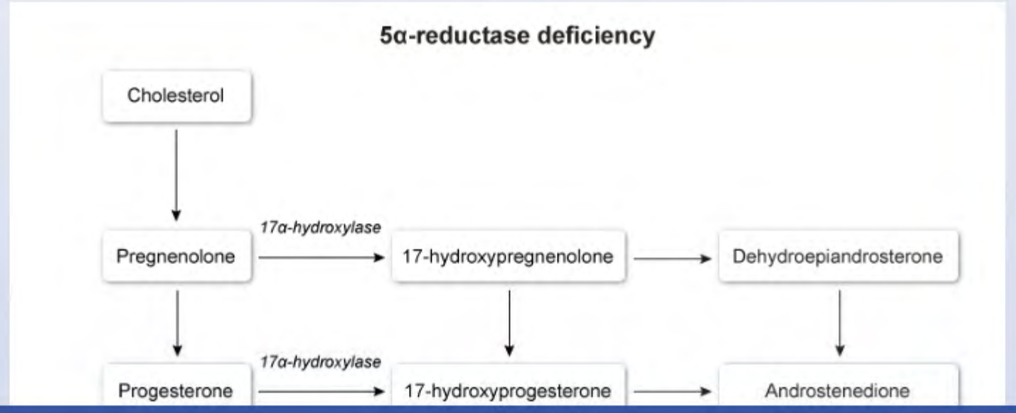
Correct

56%
Answered correctly

39 secs
Time Spent

2023
Version

Explanation



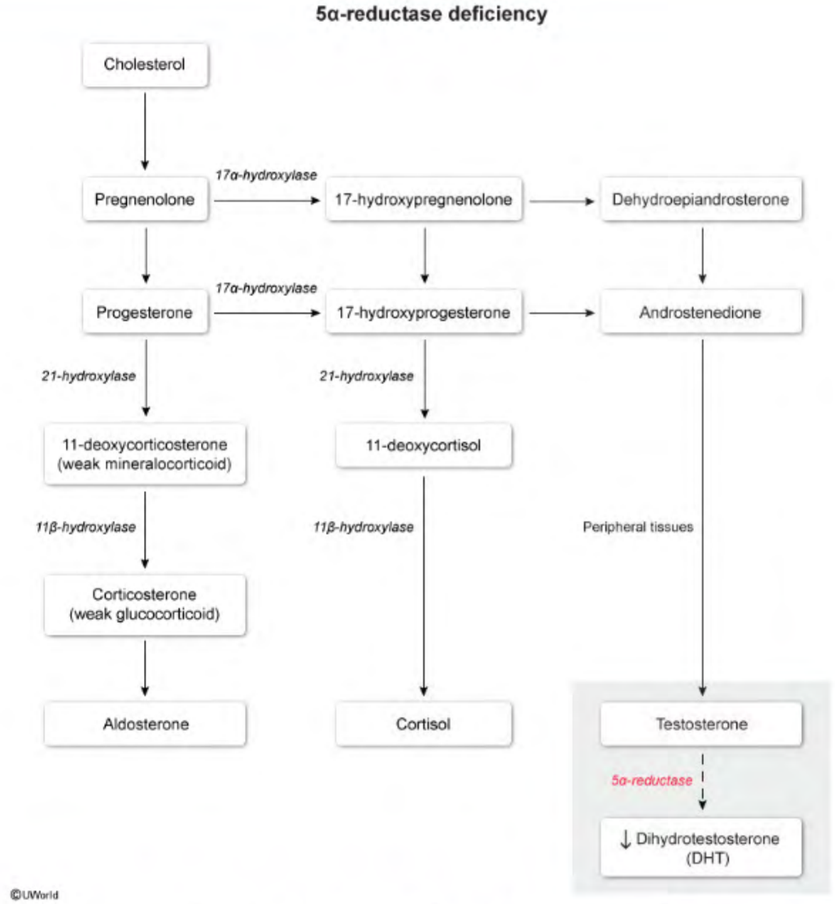
https://t.me/USMLEWorldStep1

A 22-year-old woman with no prenatal care has a normal vaginal delivery. On physical examination, the infant's extern
openi
Serum
likely h

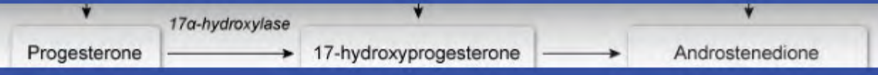
Cor

Expl

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook



https://t.me/USMLEWorldStep1

Sexual development is influenced predominantly by 3 steroid hormones:

- Testosterone**:** development of internal male genitalia (except prostate), spermatogenesis, male sexual differentiation at puberty (eg, muscle mass, libido)
- **Dihydrotestosterone** (DHT): development of **external male genitalia**, growth of **prostate**, male-pattern hair growth; also amplifies effects of testosterone due to high affinity for testosterone receptor
- Estrogen**:** endometrial proliferation, development of ovarian granulosa cells, breast development

5α-reductase converts **testosterone to DHT**. There are 2 types of 5α-reductase: type 1 is present in postpubescent skin, whereas type 2 is found predominantly in the genitals.

5α-reductase **type 2 deficiency** results in diminished conversion of testosterone to DHT in the male urogenital tract. In the phenotypically (46,XY) **male fetus** with this genetic defect, the internal genitalia (ie, testes) develop normally under the influence of testosterone. However, due to the lack of DHT, the testicles remain undescended (**cryptorchid testes** presenting as inguinal masses) and the external genitalia do not develop properly, ranging from a small phallus with hypospadias to **ambiguous or female-type genitalia**.

Testosterone levels are within the normal range because of intact negative feedback. At puberty, physiologic increased levels of testosterone and the action of 5α-reductase type 1 result in masculinization with male-pattern muscle mass, voice deepening, penile and scrotal growth, and testicular descent.

(Choice B) 17-hydroxylase deficiency results in decreased secretion of cortisol and sex steroids and an increased level of mineralocorticoids. This manifests clinically with sodium retention, leading to hypertension, and undervirilization of male infants due to low testosterone.

(Choice C) 21-hydroxylase deficiency causes corticosteroid precursors to be shunted toward androgen production, resulting in virilization of the female fetus and salt wasting. Male children have normal genitalia.

(Choice D) Aromatase catalyzes the conversion of androgens to estrogens in the gonads and peripheral tissues. Aromatase deficiency presents with virilization of female infants; male patients are not affected phenotypically.

(Choice E) Dehydroepiandrosterone (DHEA) sulfate is a weak androgen produced by the adrenal cortex. Deficiency of DHEA sulfatase does not result in undervirilization of the male fetus.

https://t.me/USMLEWorldStep1

- Estrogen: endometrial proliferation, development of ovarian granulosa cells, breast development

5α-reductase converts **testosterone to DHT**. There are 2 types of 5α-reductase: type 1 is present in postpubescent skin, whereas type 2 is found predominantly in the genitals.

5α-reductase **type 2 deficiency** results in diminished conversion of testosterone to DHT in the male urogenital tract. In the phenotypically (46,XY) **male fetus** with this genetic defect, the internal genitalia (ie, testes) develop normally under the influence of testosterone. However, due to the lack of DHT, the testicles remain undescended (**cryptorchid testes** presenting as inguinal masses) and the external genitalia do not develop properly, ranging from a small phallus with hypospadias to **ambiguous or female-type genitalia**.

Testosterone levels are within the normal range because of intact negative feedback. At puberty, physiologic increased levels of testosterone and the action of 5α-reductase type 1 result in masculinization with male-pattern muscle mass, voice deepening, penile and scrotal growth, and testicular descent.

(Choice B) 17-hydroxylase deficiency results in decreased secretion of cortisol and sex steroids and an increased level of mineralocorticoids. This manifests clinically with sodium retention, leading to hypertension, and undervirilization of male infants due to low testosterone.

(Choice C) 21-hydroxylase deficiency causes corticosteroid precursors to be shunted toward androgen production, resulting in virilization of the female fetus and salt wasting. Male children have normal genitalia.

(Choice D) Aromatase catalyzes the conversion of androgens to estrogens in the gonads and peripheral tissues. Aromatase deficiency presents with virilization of female infants; male patients are not affected phenotypically.

(Choice E) Dehydroepiandrosterone (DHEA) sulfate is a weak androgen produced by the adrenal cortex. Deficiency of DHEA sulfatase does not result in undervirilization of the male fetus.

Educational objective:
5α-reductase converts testosterone to dihydrotestosterone, which mediates development of the external genitalia in the male fetus. Male neonates with 5α-reductase deficiency are born with ambiguous genitalia that typically masculinize at puberty.

Physiology	Endocrine, Diabetes & Metabolism	Sexual differentiation
Subject	System	Topic

https://t.me/USMLEWorldStep1

Sexual development is influenced predominantly by 3 steroid hormones:

- T
  d
- **D**
  g
- E

5α-red
postpu

5α-red
tract.
norma
(**crypt**
from a

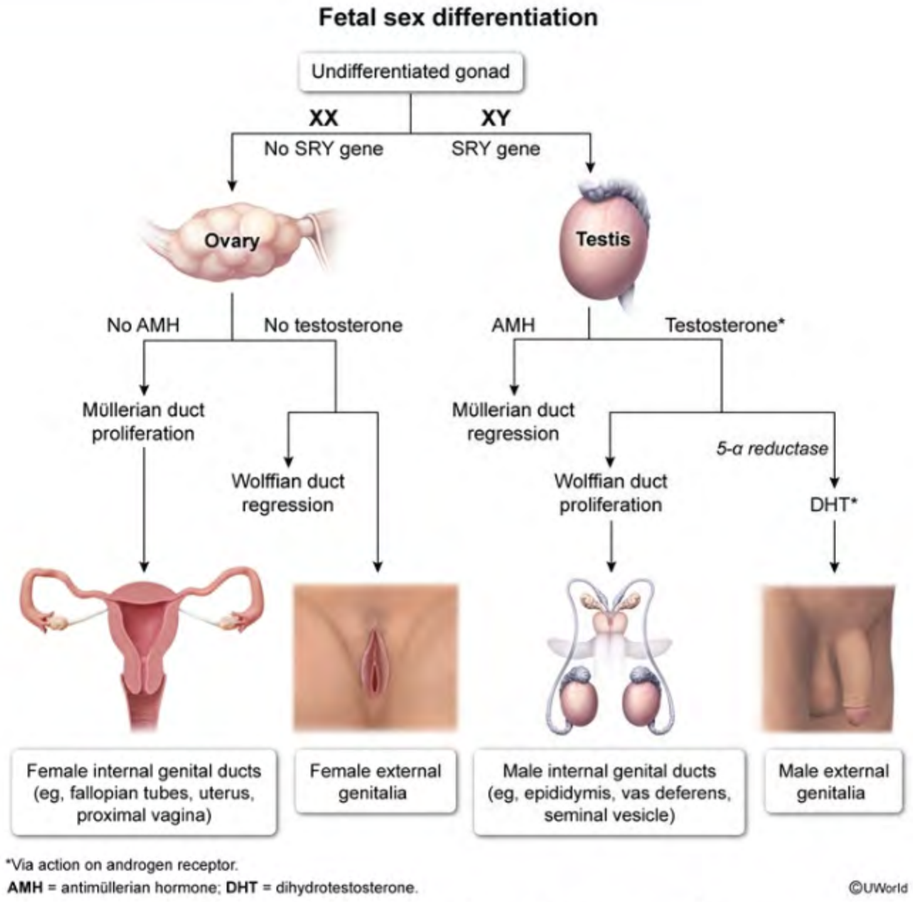
Testos
increa
muscl

(Choi
level c
underv

(Choi
produc

(Choi
Aroma

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

(Choice E) Dehydroepiandrosterone (DHEA) sulfate is a weak androgen produced by the adrenal cortex. Deficiency of DHEA sulfatase does not result in undervirilization of the male fetus.

https://t.me/USMLEWorldStep1

Sexual development is influenced predominantly by 3 steroid hormones:

- T
  d
- **D**
  g
- E

5α-red
postpu

5α-red
tract.
norma
(**crypt**
from a

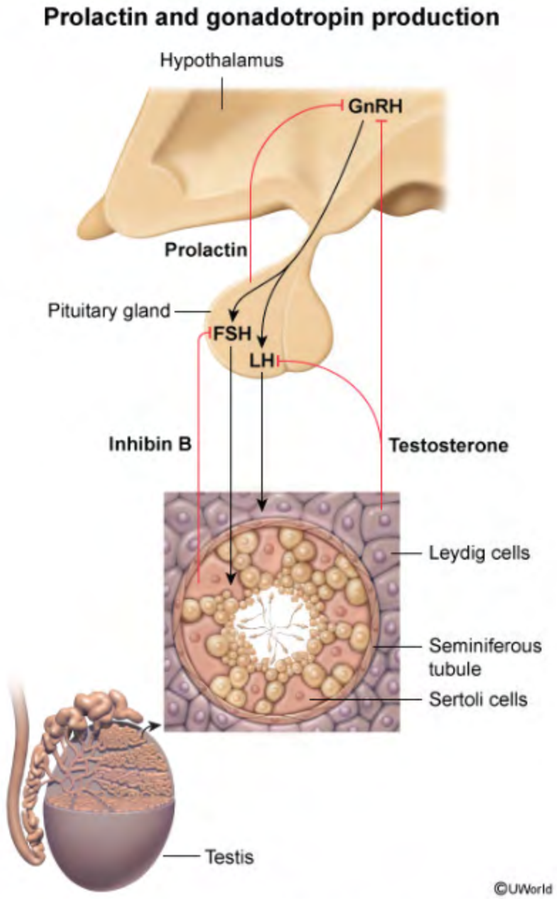
Testos
increa
muscl

(Choi
level c
underv

(Choi
produc

(Choi
Aroma

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

(Choice E) Dehydroepiandrosterone (DHEA) sulfate is a weak androgen produced by the adrenal cortex. Deficiency of DHEA sulfatase does not result in undervirilization of the male fetus.

https://t.me/USMLEWorldStep1

Sexual development is influenced predominantly by 3 steroid hormones:

- T
  d
- **D**
  g
- E

5α-red
postpu

5α-red
tract.
norma
(**crypt**
from a

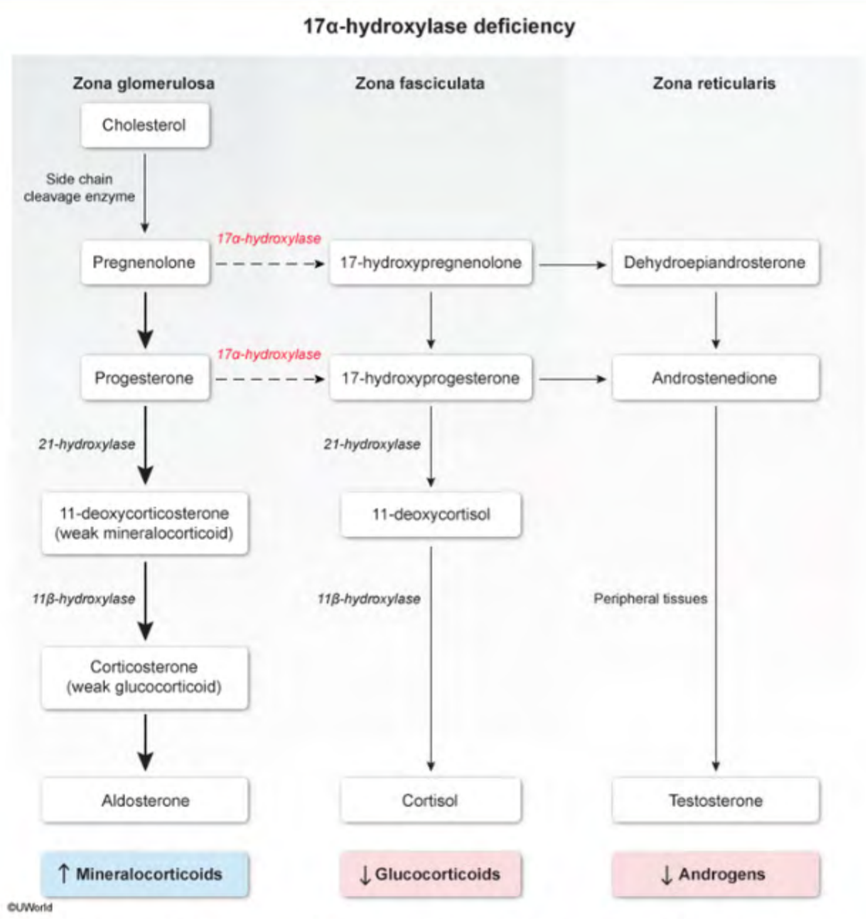
Testos
increa
muscl

(Choi
level c
underv

(Choi
produc

(Choi
Aroma

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

(Choice E) Dehydroepiandrosterone (DHEA) sulfate is a weak androgen produced by the adrenal cortex. Deficiency of DHEA sulfatase does not result in undervirilization of the male fetus.

https://t.me/USMLEWorldStep1

- **Dihydrotestosterone** (DHT): development of **external male genitalia**, growth of **prostate**, male-pattern hair g
- E

5α-red
postpu

5α-red
tract.
norma
(**crypt**
from a

Testos
increa
muscl

(Choi
level c
under

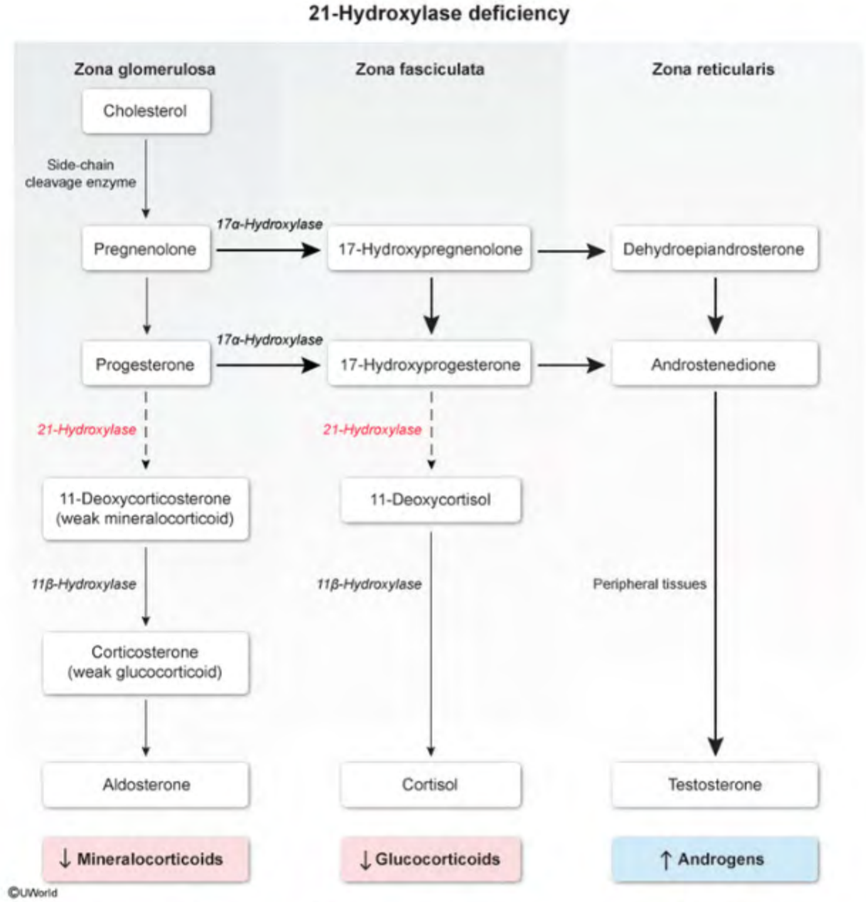
(Choi
produc

(Choi
Aroma

(Choi
Deficie

Educa
5α-reductase converts testosterone to dihydrotestosterone, which mediates development of the external genitalia in the male fetus. Male neonates with 5α-reductase deficiency are born with ambiguous genitalia that typically

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

- **Dihydrotestosterone** (DHT): development of **external male genitalia**, growth of **prostate**, male-pattern hair g
- E

5α-red
postpu

5α-red
tract.
norma
(**crypt**
from a

Testos
increa
muscl

(Choi
level c
under

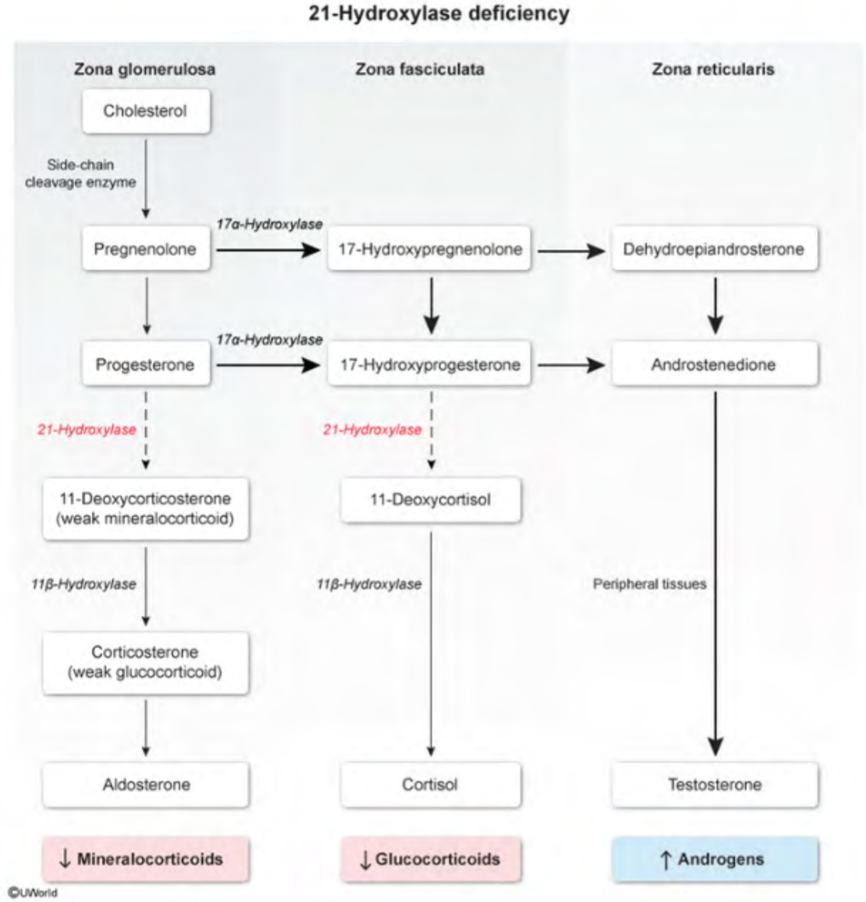
(Choi
produc

(Choi
Aroma

(Choi
Deficie

Educa
5α-reductase converts testosterone to dihydrotestosterone, which mediates development of the external genitalia in the male fetus. Male neonates with 5α-reductase deficiency are born with ambiguous genitalia that typically

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

A 72-year-old man is hospitalized for cough, purulent sputum, and shortness of breath. His medical conditions include type 2 diabetes and hypertension. A chest x-ray reveals right lower lobe pneumonia, and treatment is started with supplemental oxygen and antibiotics. While hospitalized, the patient develops persistent sinus tachycardia. Thyroid function tests ordered during the subsequent work up reveal:

Thyroid-stimulating hormone (TSH)	1.3 mU/L (normal: 0.5-5.0 mU/L)
Free thyroxine (T4)	1.2 ng/dL (normal: 0.9-2.4 ng/dL)
Triiodothyronine (T3), total	60 ng/dL (normal: 115-190 ng/dL)

Which of the following is the primary contributor to the decreased total T3 level in this patient?

- A. Decreased conversion of T4 to T3 in peripheral tissue
- B. Decreased iodination of thyroglobulin
- C. Decreased T3 production in the thyroid gland
- D. Iodine deficiency
- E. Pituitary resistance to thyrotropin-releasing hormone

Submit

https://t.me/USMLEWorldStep1

A 72-year-old man is hospitalized for cough, purulent sputum, and shortness of breath. His medical conditions include type 2 diabetes and hypertension. A chest x-ray reveals right lower lobe pneumonia, and treatment is started with supplemental oxygen and antibiotics. While hospitalized, the patient develops persistent sinus tachycardia. Thyroid function tests ordered during the subsequent work up reveal:

Thyroid-stimulating hormone (TSH)	1.3 mU/L (normal: 0.5-5.0 mU/L)
Free thyroxine (T4)	1.2 ng/dL (normal: 0.9-2.4 ng/dL)
Triiodothyronine (T3), total	60 ng/dL (normal: 115-190 ng/dL)

Which of the following is the primary contributor to the decreased total T3 level in this patient?

- ✓ A. Decreased conversion of T4 to T3 in peripheral tissue (86%)
- ✗ B. Decreased iodination of thyroglobulin (5%)
- C. Decreased T3 production in the thyroid gland (4%)
- D. Iodine deficiency (2%)
- E. Pituitary resistance to thyrotropin-releasing hormone (1%)

Incorrect
Correct answer
A

86%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

Euthyroid sick syndrome (low T3 syndrome)	
Clinical presentation	• Abnormal thyroid function tests in acutely ill patient • Mild central hypothyroid state; asymptomatic

https://t.me/USMLEWorldStep1

Euthyroid sick syndrome (low T3 syndrome)	
Clinical presentation	• Abnormal thyroid function tests in acutely ill patient • Mild central hypothyroid state; asymptomatic
Pathophysiology	• Suppression of 5'-deiodinase by glucocorticoids and inflammatory cytokines (eg, TNF-alpha, IL-1, IFN-beta) • Decreased peripheral conversion of T4 to T3 • Decreased hypothalamic TRH secretion
Diagnostic testing	• Early: Low T3, normal TSH & T4 • Late: Low T3, TSH & T4
IFN = interferon; **IL** = interleukin; **TNF** = tumor necrosis factor; **TRH** = thyrotropin-releasing hormone.	

This patient has **euthyroid sick syndrome** (ESS) (also known as low T3 syndrome), characterized by a **low T3 level**, normal thyroid-stimulating hormone (TSH), and normal T4. Thyroid hormone is released primarily in the form of T4, with conversion to T3 (the more active form) by 5'-deiodinase (types I and II) in peripheral tissues. In **severe illness**, high levels of cortisol, inflammatory cytokines, and free fatty acids **suppress deiodination of T4**, resulting in lower circulating levels of T3. Concurrently, upregulation of 5'-deiodinase type III leads to increased conversion of T4 to reverse T3 (inactive form).

ESS is thought to be a form of **mild, transient central hypothyroidism**, intended to **decrease maladaptive catabolism** in severe illness; treatment with exogenous thyroid hormone does not improve outcomes and is not indicated. With increasing duration and severity of illness, central production of thyrotropin-releasing hormone (TRH) and TSH are also suppressed, leading to lower circulating TSH and T4 levels.

(Choice B) Thyroglobulin is iodinated by thyroperoxidase (TPO) in follicular colloid. TPO activity is increased by TSH and suppressed by thioamides (eg, methimazole, propylthiouracil). Although TSH (and therefore iodination of thyroglobulin) falls in later ESS, this patient's TSH is normal, and his normal T4 level suggests adequate iodination.

(Choice C) Although a small amount of T3 is produced in the thyroid (from T4 via 5'-deiodinase type II), most is

https://t.me/USMLEWorldStep1

severe illness, high levels of cortisol, inflammatory cytokines, and free fatty acids **suppress deiodination of T4**, resulting in lower circulating levels of T3. Concurrently, upregulation of 5'-deiodinase type III leads to increased conversion of T4 to reverse T3 (inactive form).

ESS is thought to be a form of **mild, transient central hypothyroidism**, intended to **decrease maladaptive catabolism** in severe illness; treatment with exogenous thyroid hormone does not improve outcomes and is not indicated. With increasing duration and severity of illness, central production of thyrotropin-releasing hormone (TRH) and TSH are also suppressed, leading to lower circulating TSH and T4 levels.

(Choice B) Thyroglobulin is iodinated by thyroperoxidase (TPO) in follicular colloid. TPO activity is increased by TSH and suppressed by thioamides (eg, methimazole, propylthiouracil). Although TSH (and therefore iodination of thyroglobulin) falls in later ESS, this patient's TSH is normal, and his normal T4 level suggests adequate iodination.

(Choice C) Although a small amount of T3 is produced in the thyroid (from T4 via 5'-deiodinase type II), most is produced in peripheral tissues. The fall in circulating T3 levels in ESS is primarily due to suppression of peripheral conversion.

(Choice D) Iodine deficiency is rare in developed countries. When it occurs, it presents chronically with goiter and primary hypothyroidism (ie, elevated TSH, low T4). This patient has a normal TSH level, making iodine deficiency unlikely.

(Choice E) Proinflammatory cytokines decrease TSH levels by reducing secretion of TRH in the hypothalamus. In patients with ESS, TSH increases normally following administration of exogenous TRH, suggesting an intact pituitary response to TRH.

Educational objective:
Euthyroid sick syndrome (ESS) is a common pattern of thyroid function markers seen in severely ill patients. It is characterized by decreased conversion of T4 to T3 in peripheral tissues. Initial findings include a low T3 level, but later, T4 and thyroid-stimulating hormone levels may also decrease. ESS may represent a mild central hypothyroid state, which functions to minimize catabolism in severe illness.

Physiology	Endocrine, Diabetes & Metabolism	Euthyroid sick syndrome
Subject	System	Topic

https://t.me/USMLEWorldStep1

Diagnostic testing	• Early: Low T3, normal TSH & T4 Late: Low T3, TSH & T4
IFN	

Exhibit Display

This p
level,
form o
severe
resulti
conver

ESS is
catab
indicat
(TRH)

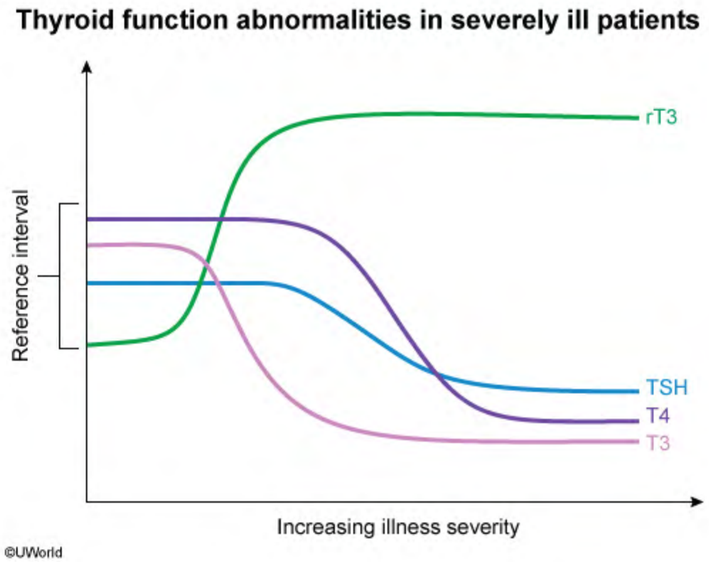
(Choi
TSH a
thyrog

(Choi
produc
conver

(Choi
primar
unlikel

(Choi
patien
pituitary response to TRH.

Educational objective:



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

Diagnostic testing	• Early: Low T3, normal TSH & T4 • Late: Low T3, TSH & T4
IFN	

This p
level,
form o
severe
resulti
conver

ESS is
catab
indicat
(TRH)

(Choi
TSH a
thyrog

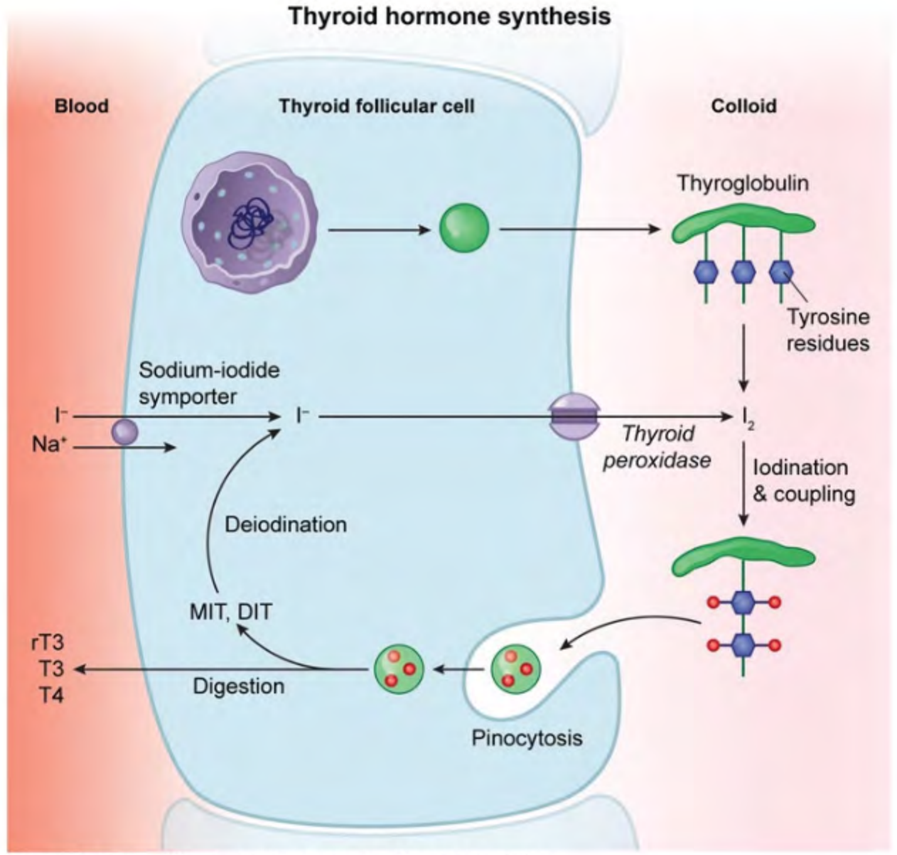
(Choi
produc
conver

(Choi
primar
unlikel

(Choi
patien
pituitary response to TRH.

Educational objective:

Exhibit Display



DIT = diiodotyrosine; **rT3** = reverse triiodothyronine; **T3** = triiodothyronine; **T4** = thyroxine; **MIT** = monoiodotyrosine.

©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

A 29-year-old woman comes to the office due to increased hair loss. She delivered a healthy baby boy 8 months ago and has not felt the same since. The patient has fatigue and decreased libido, and her menstrual cycles have not returned. She has no prior medical problems and no drug allergies. The patient takes a multivitamin and does not use tobacco, alcohol, or illicit drugs. There is no significant family history. Blood pressure is 110/70 mm Hg and pulse is 58/min. Physical examination shows diffuse alopecia and thickened, brittle nails. The thyroid is nontender. Laboratory results show decreased serum TSH and free thyroxine (T4) levels. Which of the following is the most likely diagnosis in this patient?

- A. Chronic autoimmune (Hashimoto) thyroiditis
- B. Graves disease
- C. Postpartum thyroiditis
- D. Secondary hyperthyroidism
- E. Secondary hypothyroidism
- F. Subacute granulomatous (de Quervain) thyroiditis

Submit

https://t.me/USMLEWorldStep1

A 29-year-old woman comes to the office due to increased hair loss. She delivered a healthy baby boy 8 months ago and has not felt the same since. The patient has fatigue and decreased libido, and her menstrual cycles have not returned. She has no prior medical problems and no drug allergies. The patient takes a multivitamin and does not use tobacco, alcohol, or illicit drugs. There is no significant family history. Blood pressure is 110/70 mm Hg and pulse is 58/min. Physical examination shows diffuse alopecia and thickened, brittle nails. The thyroid is nontender. Laboratory results show decreased serum TSH and free thyroxine (T4) levels. Which of the following is the most likely diagnosis in this patient?

- A. Chronic autoimmune (Hashimoto) thyroiditis
- B. Graves disease
- C. Postpartum thyroiditis
- D. Secondary hyperthyroidism
- E. Secondary hypothyroidism
- F. Subacute granulomatous (de Quervain) thyroiditis

Submit

https://t.me/USMLEWorldStep1

A 29-year-old woman comes to the office due to increased hair loss. She delivered a healthy baby boy 8 months ago and has not felt the same since. The patient has fatigue and decreased libido, and her menstrual cycles have not returned. She has no prior medical problems and no drug allergies. The patient takes a multivitamin and does not use tobacco, alcohol, or illicit drugs. There is no significant family history. Blood pressure is 110/70 mm Hg and pulse is 58/min. Physical examination shows diffuse alopecia and thickened, brittle nails. The thyroid is nontender. Laboratory results show decreased serum TSH and free thyroxine (T4) levels. Which of the following is the most likely diagnosis in this patient?

- A. Chronic autoimmune (Hashimoto) thyroiditis (4%)
- B. Graves disease (1%)
- C. Postpartum thyroiditis (31%)
- ✗ D. Secondary hyperthyroidism (2%)
- ✓ E. Secondary hypothyroidism (59%)
- F. Subacute granulomatous (de Quervain) thyroiditis (1%)

Incorrect
Correct answer
E

59%
Answered correctly

08 secs
Time Spent

2023
Version

Explanation

Central hypothyroidism	
Causes	• Mass lesions (eg, pituitary adenoma) • Pituitary surgery, trauma, irradiation • Infiltrative disorders (eg, sarcoidosis, hemochromatosis) • Pituitary infarction (eg, Sheehan syndrome)

https://t.me/USMLEWorldStep1

Explanation

Central hypothyroidism	
Causes	• Mass lesions (eg, pituitary adenoma) • Pituitary surgery, trauma, irradiation • Infiltrative disorders (eg, sarcoidosis, hemochromatosis) • Pituitary infarction (eg, Sheehan syndrome)
Clinical features	• Hypothyroid symptoms • Mass-effect symptoms (eg, headache, visual field defects) if due to mass
Hormone levels	• Low free thyroxine (T4) • Low or inappropriately normal TSH • Other pituitary hormone deficiencies (eg, ACTH, prolactin, gonadotropins)

This patient has hypothyroidism manifesting as fatigue, hair loss, and brittle nails with a low serum thyroxine (T4) level. The **low TSH** confirms that this is due to hypothalamic-pituitary dysfunction (ie, **central/secondary hypothyroidism**) rather than a primary thyroid disorder, which would cause a compensatory rise in TSH. Central hypothyroidism is much less common than primary hypothyroidism. However, when it occurs, other hypothalamic-pituitary systems may be affected and patients may develop deficiencies of other pituitary hormones (eg, low gonadotropin levels leading to amenorrhea).

The causes of central hypothyroidism are the same as those of hypopituitarism in general. **Sheehan syndrome** is ischemic necrosis of the pituitary gland and is typically caused by systemic hypotension during delivery. During pregnancy, the pituitary gland enlarges due to estrogen-induced hyperplasia of lactotrophs, but the blood supply does not increase proportionally. Subsequent **peripartum hemorrhage with hypotension** can cause underperfusion of the pituitary gland with subsequent ischemic injury.

(Choices A and C) Chronic autoimmune (Hashimoto) thyroiditis is the most common cause of hypothyroidism. Postpartum thyroiditis is a variant of Hashimoto thyroiditis that occurs within a year of pregnancy. These disorders

https://t.me/USMLEWorldStep1

The causes of central hypothyroidism are the same as those of hypopituitarism in general. **Sheehan syndrome** is ischemic necrosis of the pituitary gland and is typically caused by systemic hypotension during delivery. During pregnancy, the pituitary gland enlarges due to estrogen-induced hyperplasia of lactotrophs, but the blood supply does not increase proportionally. Subsequent **peripartum hemorrhage with hypotension** can cause underperfusion of the pituitary gland with subsequent ischemic injury.

(Choices A and C) Chronic autoimmune (Hashimoto) thyroiditis is the most common cause of hypothyroidism. Postpartum thyroiditis is a variant of Hashimoto thyroiditis that occurs within a year of pregnancy. These disorders cause primary hypothyroidism with elevated TSH levels.

(Choice B) Graves disease is an autoimmune disorder caused by activating antibodies against the TSH receptor. It presents with elevated T4 and suppressed TSH levels, typically with a goiter and ocular manifestations (eg, proptosis, lid lag).

(Choice D) Secondary (central) hyperthyroidism is a rare disorder, usually caused by a TSH-secreting pituitary adenoma. Both TSH and serum T4 levels are elevated.

(Choice F) Subacute granulomatous (de Quervain) thyroiditis causes a painful goiter and transient hyperthyroid symptoms; it typically follows a viral syndrome.

Educational objective:
Central hypothyroidism is characterized by low serum TSH and thyroxine (T4) levels and is due to hypothalamic-pituitary dysfunction. Sheehan syndrome is ischemic necrosis of the pituitary gland and is typically caused by systemic hypotension during delivery. In addition to central hypothyroidism, patients may also develop deficiencies of other pituitary hormones (eg, ACTH, prolactin, gonadotropins).

References

- Clinical review: central hypothyroidism: pathogenic, diagnostic, and therapeutic challenges.

Pathophysiology	Endocrine, Diabetes & Metabolism	Hypothyroidism
Subject	System	Topic

Copyright © UWorld. All rights reserved.

https://t.me/USMLEWorldStep1

A 6-year-old boy is brought to the emergency department after a traumatic fall from his bicycle. Physical examination shows a large laceration over his left leg that is irrigated and closed with sutures. While he is receiving care, a routine blood draw shows milky plasma that forms a creamy-appearing supernatant upon standing. Further testing shows that his plasma lipoprotein lipase activity measured after intravenous heparin administration is substantially lower than normal. If his condition remains untreated, this patient is most likely to develop which of the following features?

- A. Acute pancreatitis
- B. Intellectual disability
- C. Myocardial infarction
- D. Tendon xanthomas
- E. Xanthelasmas

Submit

https://t.me/USMLEWorldStep1

A 6-year-old boy is brought to the emergency department after a traumatic fall from his bicycle. Physical examination shows a large laceration over his left leg that is irrigated and closed with sutures. While he is receiving care, a routine blood draw shows milky plasma that forms a creamy-appearing supernatant upon standing. Further testing shows that his plasma lipoprotein lipase activity measured after intravenous heparin administration is substantially lower than normal. If his condition remains untreated, this patient is most likely to develop which of the following features?

- ✓ A. Acute pancreatitis (38%)
- B. Intellectual disability (1%)
- C. Myocardial infarction (20%)
- D. Tendon xanthomas (24%)
- E. Xanthelasmas (14%)

Correct

38% Answered correctly

03 secs Time Spent

2023 Version

Explanation

Important inherited hyperlipoproteinemias

Dyslipidemia	Protein defect	Elevated lipoproteins	Major manifestations
Familial chylomicronemia syndrome (type I)	• Lipoprotein lipase • ApoC-2	Chylomicrons	• Acute pancreatitis • Lipemia retinalis • Eruptive xanthomas
Familial			• Premature atherosclerosis

https://t.me/USMLEWorldStep1

Important inherited hyperlipoproteinemias			
Dyslipidemia	**Protein defect**	**Elevated lipoproteins**	**Major manifestations**
Familial chylomicronemia syndrome (type I)	• Lipoprotein lipase • ApoC-2	Chylomicrons	• Acute pancreatitis • Lipemia retinalis • Eruptive xanthomas
Familial hypercholesterolemia (type II A)	• LDL receptor • ApoB-100	LDL	• Premature atherosclerosis • Tendon xanthomas • Xanthelasmas
Familial dysbetalipoproteinemia (type III)	• ApoE	Chylomicron & VLDL remnants	• Premature atherosclerosis • Tuboeruptive & palmar xanthomas
Familial hypertriglyceridemia (type IV)	• Polygenic	VLDL	• Associated with coronary disease, pancreatitis & diabetes
LDL = low-density lipoprotein; **VLDL** = very low-density lipoprotein.			

This patient has **familial chylomicronemia syndrome** (type 1 hyperlipoproteinemia), an autosomal recessive condition most often caused by **lipoprotein lipase (LPL) deficiency**. LPL is normally bound to heparan sulfate moieties on the vascular endothelium, allowing it to interact with chylomicrons and VLDL in the circulation and release free fatty acids into the adjacent tissues. Heparin administration releases these endothelium-bound lipases, allowing LPL activity to be measured in the laboratory. Without sufficient LPL activity, the body is unable to clear dietary lipid loads due to defective hydrolysis of serum triglycerides (especially **chylomicrons**).

Patients with familial chylomicronemia syndrome present in childhood with marked **hypertriglyceridemia**, recurrent **acute pancreatitis, lipemia retinalis** (milky-appearing retinal vasculature), and eruptive xanthomas (small yellowish papules surrounded by erythema found mainly on extensor surfaces).

(Choice B) The familial hyperlipoproteinemias are not associated with intellectual disability.

https://t.me/USMLEWorldStep1

Familial hypertriglyceridemia (type IV)	• Polygenic	VLDL	• Associated with coronary disease, pancreatitis & diabetes
LDL = low-density lipoprotein; **VLDL** = very low-density lipoprotein.			

This patient has **familial chylomicronemia syndrome** (type 1 hyperlipoproteinemia), an autosomal recessive condition most often caused by **lipoprotein lipase (LPL) deficiency**. LPL is normally bound to heparan sulfate moieties on the vascular endothelium, allowing it to interact with chylomicrons and VLDL in the circulation and release free fatty acids into the adjacent tissues. Heparin administration releases these endothelium-bound lipases, allowing LPL activity to be measured in the laboratory. Without sufficient LPL activity, the body is unable to clear dietary lipid loads due to defective hydrolysis of serum triglycerides (especially **chylomicrons**).

Patients with familial chylomicronemia syndrome present in childhood with marked **hypertriglyceridemia**, recurrent **acute pancreatitis, lipemia retinalis** (milky-appearing retinal vasculature), and eruptive xanthomas (small yellowish papules surrounded by erythema found mainly on extensor surfaces).

(Choice B) The familial hyperlipoproteinemias are not associated with intellectual disability.

(Choices C, D, and E) Accelerated coronary artery disease, tendon xanthomas (nodular lipid deposits in the tendons, particularly the Achilles), and xanthelasmas are seen in familial hypercholesterolemia, a condition caused by defects in the LDL receptor or its ligand, ApoB-100. As LDL is mainly cleared from the circulation by receptor-mediated uptake in the liver, individuals with familial hypercholesterolemia have dramatically elevated LDL concentrations.

Educational objective:
Familial chylomicronemia syndrome frequently presents in childhood with recurrent episodes of acute pancreatitis. Patients with this disorder are not usually at increased risk for premature coronary artery disease. Eruptive skin xanthomas may be present in hypertriglyceridemia, but tendon xanthomas and xanthelasmas are primarily seen with hypercholesterolemia.

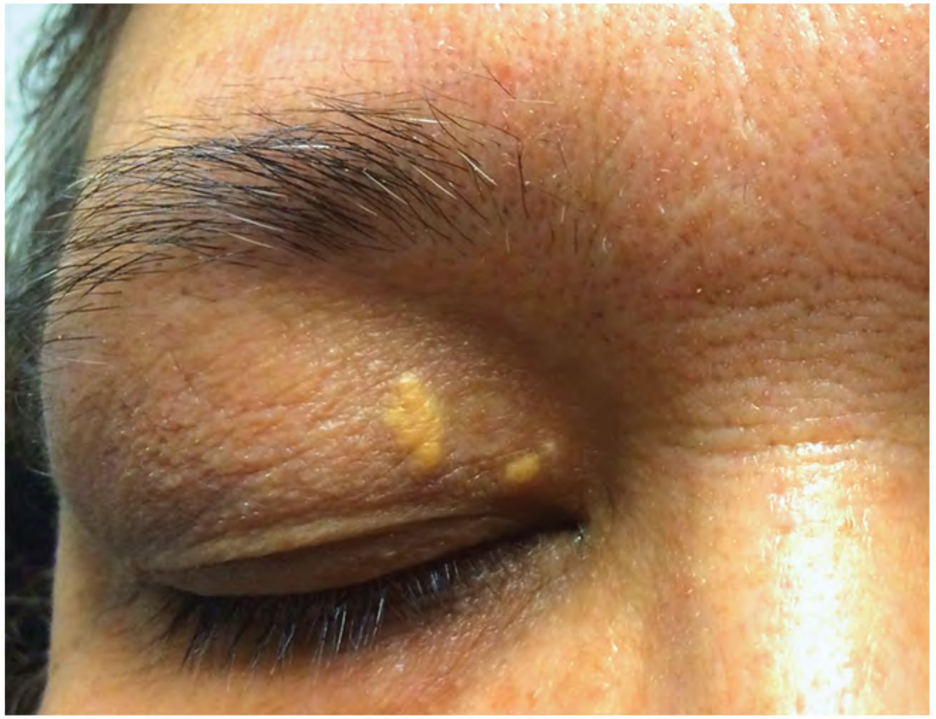
Pathology	Endocrine, Diabetes & Metabolism	Dyslipidemia
Subject	System	Topic

Copyright © UWorld. All rights reserved.

https://t.me/USMLEWorldStep1

Familial hypertriglyceridemia (type IV)	• Polygenic	VLDL	• Associated with coronary disease, pancreatitis & diabetes
LD			

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

This p
conditi
moieti
releas
lipases
clear c

Patien
recurr
(small

(Choi

(Choi
tendor
by def
media
concer

Educa
Familia
Patien
xantho
with hy

Patholog
Subject

Copyright © UWorld. All rights reserved.

https://t.me/USMLEWorldStep1

A 45-year-old man comes to the emergency department after experiencing a sudden-onset headache with brief loss of consciousness while working in his yard. CT scan of the brain reveals blood in the basal cistern from a ruptured intracranial aneurysm. The patient is hospitalized, and endovascular coiling of the aneurysm is performed. Over the next several days, his symptoms gradually improve but the patient develops worsening hyponatremia. Which of the following is the most likely cause of this patient's hyponatremia?

- A. Defective central thirst regulation
- B. Impaired renal concentrating ability
- C. Inadequate dietary sodium intake
- D. Increased antidiuretic hormone secretion
- E. Stress-induced excessive cortisol levels

Submit

https://t.me/USMLEWorldStep1

A 45-year-old man comes to the emergency department after experiencing a sudden-onset headache with brief loss of consciousness while working in his yard. CT scan of the brain reveals blood in the basal cistern from a ruptured intracranial aneurysm. The patient is hospitalized, and endovascular coiling of the aneurysm is performed. Over the next several days, his symptoms gradually improve but the patient develops worsening hyponatremia. Which of the following is the most likely cause of this patient's hyponatremia?

- A. Defective central thirst regulation (15%)
- ✗ B. Impaired renal concentrating ability (8%)
- C. Inadequate dietary sodium intake (1%)
- ✓ D. Increased antidiuretic hormone secretion (65%)
- E. Stress-induced excessive cortisol levels (8%)

Incorrect
Correct answer
D

65%
Answered correctly

05 secs
Time Spent

2023
Version

Explanation

Syndrome of inappropriate antidiuretic hormone (SIADH)	
Pathophysiology	• Uncontrolled secretion of ADH • Leads to water retention & impaired urinary water excretion
Causes	• CNS disturbances (stroke, hemorrhage, trauma) • Medications (eg, carbamazepine, SSRIs,

https://t.me/USMLEWorldStep1

Explanation

Syndrome of inappropriate antidiuretic hormone (SIADH)	
Pathophysiology	• Uncontrolled secretion of ADH • Leads to water retention & impaired urinary water excretion
Causes	• CNS disturbances (stroke, hemorrhage, trauma) • Medications (eg, carbamazepine, SSRIs, NSAIDs) • Lung disease (eg, pneumonia) • Malignancy (eg, small-cell lung cancer)
Clinical findings	• Nausea, forgetfulness (mild hyponatremia) • Seizures, coma (severe hyponatremia) • Euvolemia (eg, moist mucous membranes, no edema, no JVD)
Laboratory findings	• Hyponatremia • Low serum osmolality • High urine osmolality • High urine sodium
ADH = antidiuretic hormone; **JVD** = jugular venous distension; **SSRIs** = selective serotonin reuptake inhibitors.	

This patient likely has the syndrome of inappropriate antidiuretic hormone secretion (**SIADH**), the most common cause of **hyponatremia** following subarachnoid hemorrhage (SAH). Antidiuretic hormone (ADH) is normally

https://t.me/USMLEWorldStep1

This patient likely has the syndrome of inappropriate antidiuretic hormone secretion (**SIADH**), the most common cause of **hyponatremia** following subarachnoid hemorrhage (SAH). Antidiuretic hormone (ADH) is normally released by the hypothalamus and posterior pituitary in response to elevated serum osmolality (eg, following water deprivation) or decreased arterial blood volume.

ADH promotes renal water reabsorption, which leads to concentration of the urine and lowering of serum osmolality and serum sodium. Hypothalamic damage following SAH is thought to trigger **excessive secretion of ADH**, resulting in the classic SIADH features of **hypotonicity** (ie, low serum osmolarity), **hyponatremia**, and persistently concentrated urine (ie, **high urine osmolality**).

In addition to SIADH, hyponatremia after SAH can also be due to cerebral salt wasting (caused by increased secretion of brain natriuretic peptide, which leads to urinary sodium losses) or secondary adrenal insufficiency (eg, decreased cortisol production due to pituitary injury) **(Choice E)**. In both conditions, decreased extracellular fluid volume causes a secondary increase in ADH and worsening hyponatremia.

(Choice A) In primary polydipsia, defective central thirst regulation leads to excessive water intake and hyponatremia. ADH levels are low, rather than high. Primary polydipsia is typically seen with certain psychiatric conditions (eg, schizophrenia) or use of psychotropic medications. It is not commonly associated with SAH.

(Choice B) Impaired renal concentrating ability is seen in diabetes insipidus (DI), which occurs either due to ADH resistance (nephrogenic DI) or decreased ADH production (central DI). DI may follow cerebral injury; however, it does not cause hyponatremia. Rather, DI results in a clinical picture opposite that of SIADH, featuring hypernatremia, increased serum osmolality, and dilute urine (ie, low urine osmolality).

(Choice C) Inadequate dietary intake of sodium is a rare cause of hyponatremia primarily seen in cases of chronic alcohol abuse (eg, beer potomania). SIADH is a more likely cause of hyponatremia in this patient.

Educational objective:
Hyponatremia following cerebral injury (eg, subarachnoid hemorrhage) is most commonly due to the syndrome of inappropriate antidiuretic hormone secretion. Injury to the hypothalamus leads to increased secretion of antidiuretic hormone, which in turn leads to water retention, low serum osmolality, and increased urinary sodium excretion.

https://t.me/USMLEWorldStep1

This patient likely has the syndrome of inappropriate antidiuretic hormone secretion (**SIADH**), the most common cause releas deprivation

ADH p osmol **ADH**, persist

In add secret decrea volum

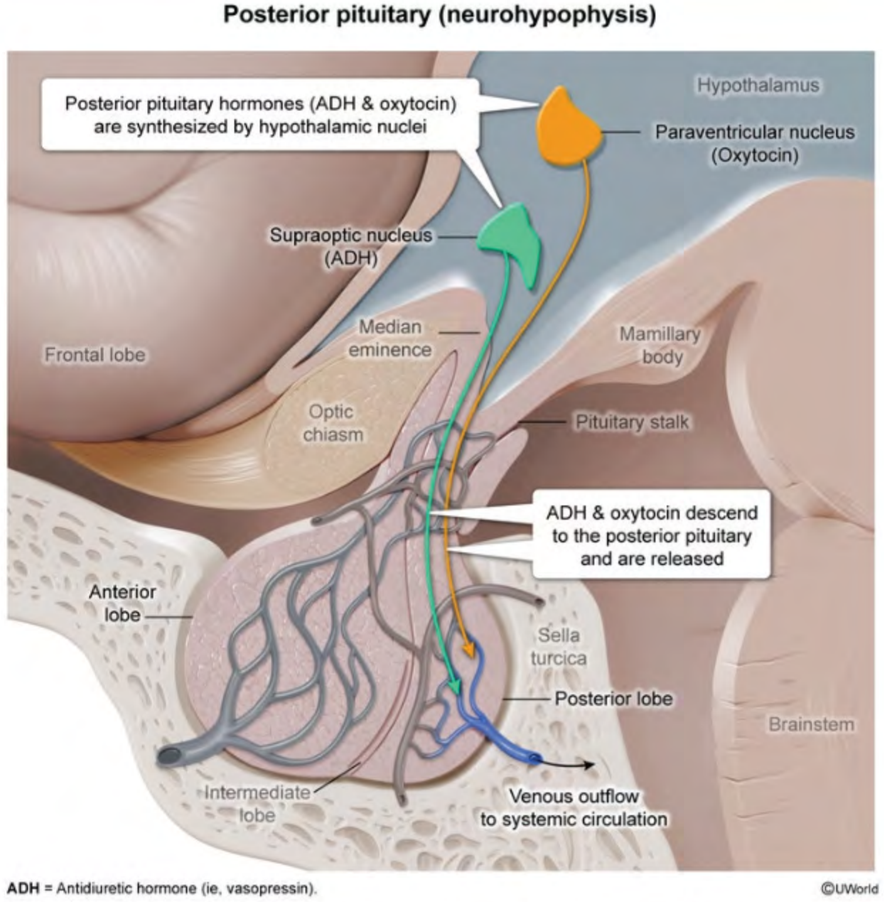
(Choi hypon condit

(Choi resista does n hyperr

(Choi alcoho

Educa Hypon inappr antidiu excretion.

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

An 18-year-old girl with a history of type 1 diabetes mellitus comes to the emergency department after several hours of nausea, vomiting, and abdominal pain. The patient reports that she is on vacation visiting friends and has not taken insulin in the last 2 days. Physical examination shows breath with fruity odor and dry mucosal membranes. Laboratory studies show a blood glucose level of 452 mg/dL and high anion gap metabolic acidosis. Urinalysis is positive for ketones. It is determined that the patient's insulin deficiency is causing increased production of gluconeogenic precursors that are subsequently converted to glucose in the liver. Which of the following enzymes is most likely to provide these precursor substrates?

- A. Acetyl CoA carboxylase
- B. Acyl CoA synthetase
- C. ATP citrate lyase
- D. Glucose-6-phosphate dehydrogenase
- E. Glycerol kinase

Submit

https://t.me/USMLEWorldStep1

An 18-year-old girl with a history of type 1 diabetes mellitus comes to the emergency department after several hours of nausea, vomiting, and abdominal pain. The patient reports that she is on vacation visiting friends and has not taken insulin in the last 2 days. Physical examination shows breath with fruity odor and dry mucosal membranes. Laboratory studies show a blood glucose level of 452 mg/dL and high anion gap metabolic acidosis. Urinalysis is positive for ketones. It is determined that the patient's insulin deficiency is causing increased production of gluconeogenic precursors that are subsequently converted to glucose in the liver. Which of the following enzymes is most likely to provide these precursor substrates?

- ✗ A. Acetyl CoA carboxylase (41%)
- B. Acyl CoA synthetase (25%)
- C. ATP citrate lyase (4%)
- D. Glucose-6-phosphate dehydrogenase (8%)
- ✓ E. Glycerol kinase (19%)

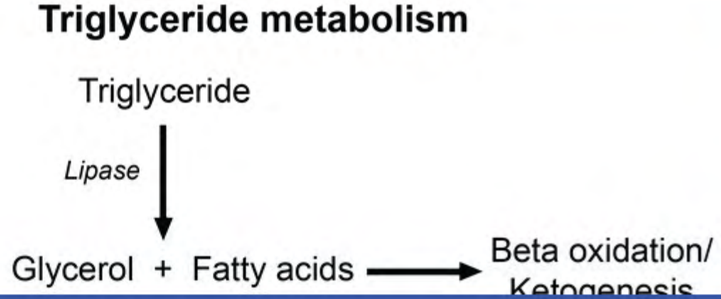
Incorrect
Correct answer
E

19%
Answered correctly

03 secs
Time Spent

2023
Version

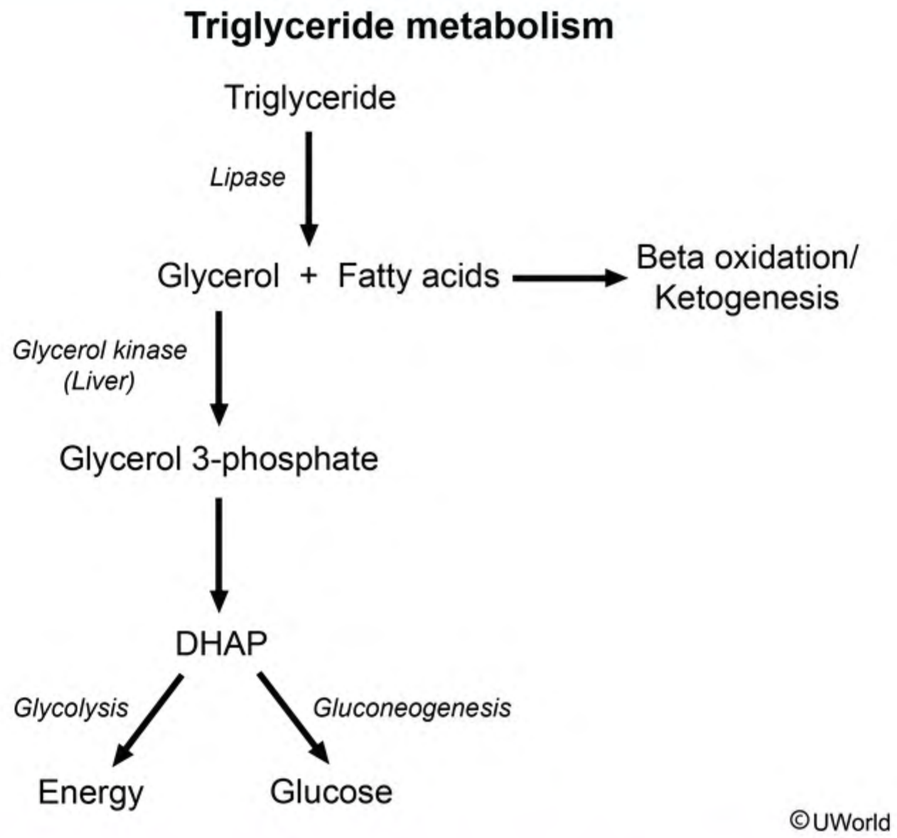
Explanation



https://t.me/USMLEWorldStep1

An 18-year-old girl with a history of type 1 diabetes mellitus comes to the emergency department after several hours
not tak
memb
Urinaly
produc
followi

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Glycerol + Fatty acids → Beta oxidation/ Ketogenesis

https://t.me/USMLEWorldStep1



©UWorld

This patient in **diabetic ketoacidosis** is experiencing increased triglyceride breakdown in adipose tissue due to her insulin deficiency. Triglycerides stored in adipose tissue are metabolized to free fatty acids and **glycerol** by hormone-sensitive lipase in response to low insulin and high catecholamine levels. Adipocytes are unable to metabolize glycerol, so it is secreted into the circulation and transported to the liver, where it is phosphorylated to glycerol-3-phosphate by **glycerol kinase**. Glycerol-3-phosphate is subsequently converted by glycerol-3-phosphate dehydrogenase to dihydroxyacetone phosphate (DHAP), which can be used to produce **glucose** through **gluconeogenesis**.

(Choice A) Acetyl CoA carboxylase is a biotin-dependent enzyme present in both liver and adipose tissues. It catalyzes the first committed step in fatty acid synthesis, the conversion of acetyl CoA to malonyl CoA.

(Choice B) Fatty acids must first be activated by acyl CoA synthetase in the cytoplasm in order to undergo beta-oxidation in mitochondria. Although beta-oxidation of fatty acids is increased in diabetic ketoacidosis, the resulting acetyl-CoA is used for energy and ketone body formation (not glucose production).

(Choice C) In contrast to fatty acid oxidation, which occurs in mitochondria, fatty acid synthesis occurs in the cytosol. Acetyl CoA generated in mitochondria during glycolysis is transferred to the cytosol as citrate. In the cytoplasm, ATP citrate lyase converts citrate back into acetyl CoA that can be used for fatty acid chain elongation.

(Choice D) Glucose-6-phosphate dehydrogenase is the first enzyme of the hexose monophosphate (HMP) shunt. The HMP shunt produces pentose sugars for nucleotide synthesis and NADPH, which is necessary for cholesterol and fatty acid biosynthesis.

Educational objective:
Glycerol produced by the degradation of triglycerides in adipose tissue can be used by glycerol kinase in the liver and kidney to synthesize glucose during gluconeogenesis.

Biochemistry	Endocrine, Diabetes & Metabolism	Triglyceride metabolism
Subject	System	Topic

Copyright © UWorld. All rights reserved.

https://t.me/USMLEWorldStep1

A 19-year-old man comes to the office due to frequent episodes of disorientation, palpitations, tremulousness, and excessive sweating over the past 3 months. The symptoms resolve quickly after he drinks juice or a sweetened beverage. The patient has type 1 diabetes mellitus diagnosed at age 12. He takes short- and long-acting insulin and has had no dose changes in the past 2 years. The patient is a college student and reports increased stress due to his examination schedule and frequent travel with the school tennis team. He does not use tobacco, alcohol, or recreational drugs. Vital signs and physical examination are within normal limits, but he has gained 3 kg (6.6 lb) since his last visit 4 months ago. Laboratory results include a hemoglobin A1c of 6.8%. Which of the following factors most likely precipitated this patient's current symptoms?

- A. Fructose-rich drink consumption
- B. Intensive exercise
- C. Mental stress
- D. Sleep deprivation
- E. Weight gain

Submit

https://t.me/USMLEWorldStep1

A 19-year-old man comes to the office due to frequent episodes of disorientation, palpitations, tremulousness, and excessive sweating over the past 3 months. The symptoms resolve quickly after he drinks juice or a sweetened beverage. The patient has type 1 diabetes mellitus diagnosed at age 12. He takes short- and long-acting insulin and has had no dose changes in the past 2 years. The patient is a college student and reports increased stress due to his examination schedule and frequent travel with the school tennis team. He does not use tobacco, alcohol, or recreational drugs. Vital signs and physical examination are within normal limits, but he has gained 3 kg (6.6 lb) since his last visit 4 months ago. Laboratory results include a hemoglobin A1c of 6.8%. Which of the following factors most likely precipitated this patient's current symptoms?

- A. Fructose-rich drink consumption (3%)
- ✓ B. Intensive exercise (51%)
- C. Mental stress (31%)
- D. Sleep deprivation (5%)
- E. Weight gain (8%)

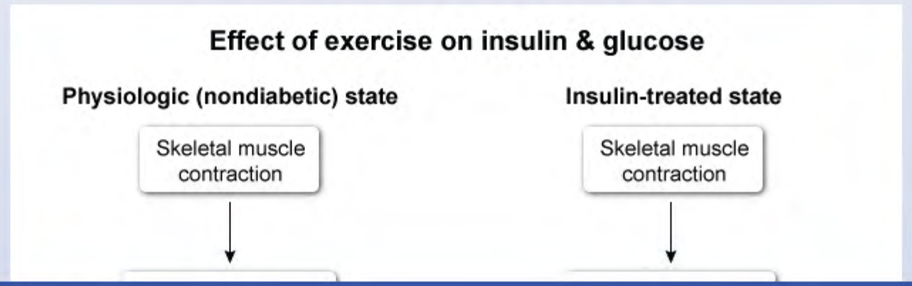
Correct

51% Answered correctly

03 secs Time Spent

2023 Version

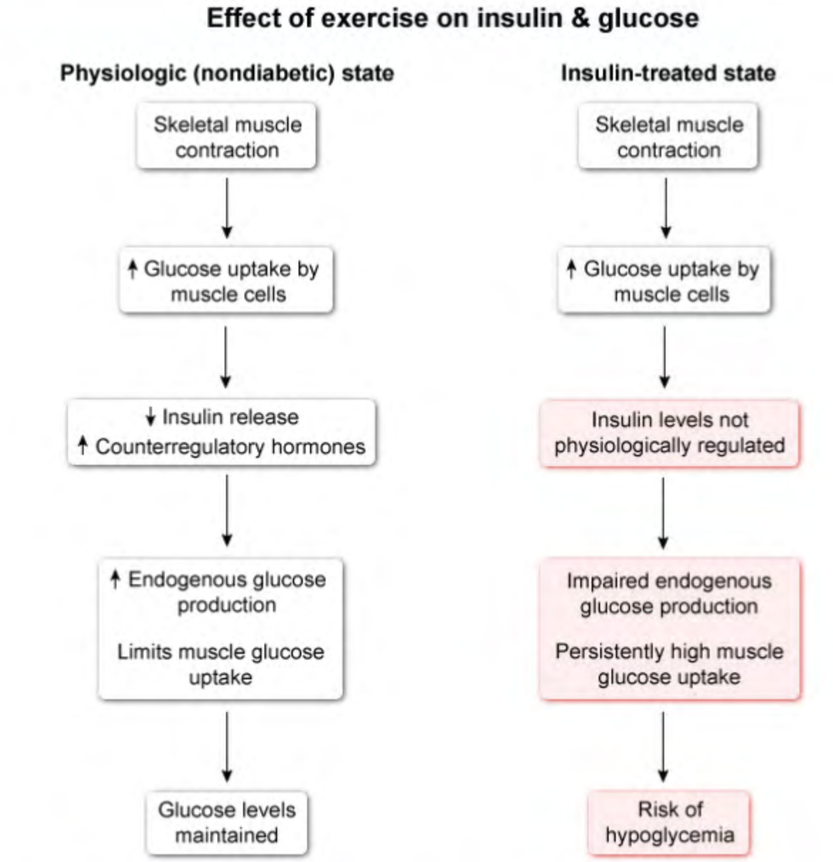
Explanation



https://t.me/USMLEWorldStep1

A 19-year-old man comes to the office due to frequent episodes of disorientation, palpitations, tremulousness, and
excess
bevera
and ha
due to
alcoho
(6.6 lb
followi

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

This patient has frequent symptomatic **hypoglycemia**—disorientation, sweating, and palpitations relieved by intake of glucose—despite making no changes to his established insulin regimen. Hypoglycemia is often induced in patients with type 1 diabetes mellitus by inadvertent overdose of insulin or decreased carbohydrate intake (eg, skipped meal) but can also be triggered by **intensive physical activity** or exercise.

Glucose uptake by skeletal muscle cells is mediated by glucose transporter type 4 (**GLUT-4**). GLUT-4 is **translocated** to cell membranes and transverse tubules (deep invaginations in the cell membrane) in response to **insulin**. GLUT-4 translocation also occurs during **muscle contraction** by an insulin-independent mechanism mediated by several cellular factors, including AMP-activated kinase, nitric oxide, and calcium-calmodulin–activated protein kinase.

In normal individuals, overt hypoglycemia does not occur with exercise because a drop in blood glucose suppresses insulin release from the beta cells, and counterregulatory hormones (eg, glucagon) increase endogenous glucose production via glycogenolysis and gluconeogenesis. However, patients taking **exogenous insulin** are vulnerable to exercise-induced hypoglycemia because insulin **continues to be released** from the injection site despite falling glucose levels.

(Choice A) Patients with hereditary fructose intolerance cannot break down fructose. They develop hypoglycemia and vomiting after ingestion of fructose-containing foods. However, this condition typically presents at the age of weaning (when fructose is introduced), and patients often develop a protective distaste for sweets. Ingestion of a fructose-containing drink would worsen the hypoglycemia, not correct it.

(Choices C and D) Significant stressors such as severe mental or emotional distress, sleep deprivation, infection, and pain tend to cause hyperglycemia rather than hypoglycemia due to increased production of counterregulatory hormones (eg, catecholamines, cortisol). These hormones raise the glucose level by increasing glycogenolysis and gluconeogenesis and decreasing pancreatic insulin secretion (in patients with residual islet cell function).

(Choice E) Weight gain is associated with insulin resistance. Patients treated with insulin who gain weight usually develop hyperglycemia and require increased doses of insulin to maintain control of glucose.

Educational objective:
Uptake of glucose by skeletal muscle is mediated by glucose transporter type 4, which is translocated to the cell

https://t.me/USMLEWorldStep1

in patients with type 1 diabetes mellitus by inadvertent overdose of insulin or decreased carbohydrate intake (eg, skipped meal) but can also be triggered by **intensive physical activity** or exercise.

Glucose uptake by skeletal muscle cells is mediated by glucose transporter type 4 (**GLUT-4**). GLUT-4 is **translocated** to cell membranes and transverse tubules (deep invaginations in the cell membrane) in response to **insulin**. GLUT-4 translocation also occurs during **muscle contraction** by an insulin-independent mechanism mediated by several cellular factors, including AMP-activated kinase, nitric oxide, and calcium-calmodulin–activated protein kinase.

In normal individuals, overt hypoglycemia does not occur with exercise because a drop in blood glucose suppresses insulin release from the beta cells, and counterregulatory hormones (eg, glucagon) increase endogenous glucose production via glycogenolysis and gluconeogenesis. However, patients taking **exogenous insulin** are vulnerable to exercise-induced hypoglycemia because insulin **continues to be released** from the injection site despite falling glucose levels.

(Choice A) Patients with hereditary fructose intolerance cannot break down fructose. They develop hypoglycemia and vomiting after ingestion of fructose-containing foods. However, this condition typically presents at the age of weaning (when fructose is introduced), and patients often develop a protective distaste for sweets. Ingestion of a fructose-containing drink would worsen the hypoglycemia, not correct it.

(Choices C and D) Significant stressors such as severe mental or emotional distress, sleep deprivation, infection, and pain tend to cause hyperglycemia rather than hypoglycemia due to increased production of counterregulatory hormones (eg, catecholamines, cortisol). These hormones raise the glucose level by increasing glycogenolysis and gluconeogenesis and decreasing pancreatic insulin secretion (in patients with residual islet cell function).

(Choice E) Weight gain is associated with insulin resistance. Patients treated with insulin who gain weight usually develop hyperglycemia and require increased doses of insulin to maintain control of glucose.

Educational objective:
Uptake of glucose by skeletal muscle is mediated by glucose transporter type 4, which is translocated to the cell membrane in response to insulin and muscle contraction (via an insulin-independent mechanism). Hypoglycemia can be precipitated by exercise in patients with insulin-treated diabetes due to the persistent effects of exogenous insulin.

https://t.me/USMLEWorldStep1

A 40-year-old woman is evaluated for intermittent headaches, insomnia, diaphoresis, and unintentional weight loss over the past several months. The patient has no other medical problems and takes no medications. She does not use tobacco, alcohol, or illicit drugs and has no significant family history. The patient is found to have a neoplastic mass producing excessive amounts of hormones that are causing her symptoms. Surgical resection of the abnormal tissue is performed with no operative complications. Microscopic examination of the tumor cells shows electron-dense, membrane-bound secretory granules. Immunohistochemistry is positive for synaptophysin, chromogranin, and neuron-specific enolase. The abnormal tissue most likely originated from which of the following?

- A. Adrenal cortex
- B. Adrenal medulla
- C. Ovary
- D. Parathyroid gland
- E. Thyroid follicles

Submit

https://t.me/USMLEWorldStep1

A 40-year-old woman is evaluated for intermittent headaches, insomnia, diaphoresis, and unintentional weight loss over the past several months. The patient has no other medical problems and takes no medications. She does not use tobacco, alcohol, or illicit drugs and has no significant family history. The patient is found to have a neoplastic mass producing excessive amounts of hormones that are causing her symptoms. Surgical resection of the abnormal tissue is performed with no operative complications. Microscopic examination of the tumor cells shows electron-dense, membrane-bound secretory granules. Immunohistochemistry is positive for synaptophysin, chromogranin, and neuron-specific enolase. The abnormal tissue most likely originated from which of the following?

- A. Adrenal cortex (3%)
- ✓ B. Adrenal medulla (85%)
- C. Ovary (1%)
- D. Parathyroid gland (1%)
- E. Thyroid follicles (8%)

Correct

85% Answered correctly

03 secs Time Spent

2023 Version

Explanation

Pheochromocytoma	
Pathogenesis	• Arises from neuroendocrine cells in **adrenal medulla** • 25% inherited: ◦ *VHL* gene (von Hippel-Lindau) ◦ *RET* gene (multiple endocrine neoplasia type 2) ◦ *NF1* gene (neurofibromatosis)

https://t.me/USMLEWorldStep1

Explanation

Pheochromocytoma	
Pathogenesis	• Arises from neuroendocrine cells in **adrenal medulla** • 25% inherited: ◦ *VHL* gene (von Hippel-Lindau) ◦ *RET* gene (multiple endocrine neoplasia type 2) ◦ *NF1* gene (neurofibromatosis) • Symptoms result from **increased catecholamine secretion**
Symptoms	• Headache • Tachycardia/palpitations • Sweating • Hypertension
Rule of 10s	• 10% bilateral • 10% extraadrenal (paragangliomas) • 10% malignant
Diagnosis	Elevated urinary & plasma catecholamines & metanephrines

Pheochromocytoma is a tumor of the **chromaffin cells** of the **adrenal medulla** characterized by excess production of **catecholamines** (norepinephrine, epinephrine, dopamine). Fluctuating catecholamine release results in increased vascular tone and hypertension, often associated with episodic headache, diaphoresis, and palpitations. The diagnosis is confirmed by detecting elevated levels of urinary and plasma catecholamines and metanephrines (catecholamine breakdown products).

Histopathology shows a highly vascular tumor with nests of spindle-shaped or polygonal cells. The neurohormonal character of the cells is confirmed with stains for **synaptophysin**, **chromogranin**, and **neuron-specific enolase**, and electron microscopy may show dense membrane-bound granules containing catecholamines.

(Choices A and C) Syndromes associated with steroid hormone–producing tumors of the adrenal cortex include

https://t.me/USMLEWorldStep1

	• 10% malignant
Diagnosis	Elevated urinary & plasma catecholamines & metanephrines

Pheochromocytoma is a tumor of the **chromaffin cells** of the **adrenal medulla** characterized by excess production of **catecholamines** (norepinephrine, epinephrine, dopamine). Fluctuating catecholamine release results in increased vascular tone and hypertension, often associated with episodic headache, diaphoresis, and palpitations. The diagnosis is confirmed by detecting elevated levels of urinary and plasma catecholamines and metanephrines (catecholamine breakdown products).

Histopathology shows a highly vascular tumor with nests of spindle-shaped or polygonal cells. The neurohormonal character of the cells is confirmed with stains for **synaptophysin**, **chromogranin**, and **neuron-specific enolase**, and electron microscopy may show dense membrane-bound granules containing catecholamines.

(Choices A and C) Syndromes associated with steroid hormone-producing tumors of the adrenal cortex include hypercortisolism (Cushing syndrome), hyperaldosteronism (hypertension, hypokalemia, metabolic alkalosis), and hyperandrogenism (hirsutism, acne, androgenetic hair loss). Metabolically active ovarian tumors also can cause hyperandrogenism. Overproduction of steroid hormones is apparent on electron microscopy as well-developed smooth endoplasmic reticulum rather than membrane-bound secretory granules.

(Choice D) Parathyroid adenomas (or carcinomas) cause primary hyperparathyroidism resulting in hypercalcemia. Characteristic symptoms include constipation, abdominal pain, bone pain, and neuropsychiatric symptoms.

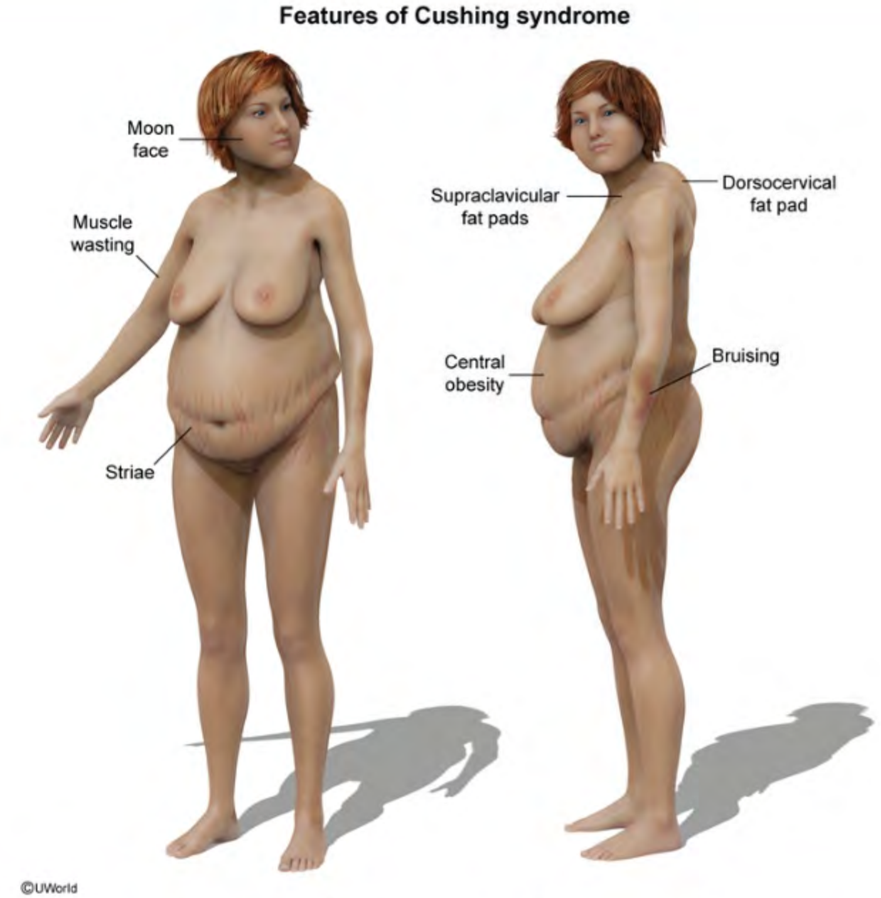
(Choice E) Toxic nodular thyroid disease could produce this patient's symptoms (eg, diaphoresis, weight loss). However, metabolically active thyroid adenomas typically show a follicular structure, with uniform cells and large amounts of follicular colloid.

Educational objective:
Pheochromocytoma is a tumor arising from the chromaffin cells of the adrenal medulla characterized by excess production of catecholamines. Clinical features include episodic hypertension, diaphoresis, and palpitations. Microscopic examination of the tumor cells shows electron-dense, membrane-bound secretory granules, and immunohistochemistry is positive for synaptophysin, chromogranin, and neuron-specific enolase.

https://t.me/USMLEWorldStep1

- 10% malignant

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Pheoc
produc
results
palpita
metan

Histop
charac
and el

(Choi
hyperc
hypera
hypera
smoot

(Choi
hyperc
sympt

(Choi
Howev
amour

Educa
Pheoc
produc
Micros
immunohistochemistry is positive for synaptophysin, chromogranin, and neuron-specific enolase.

https://t.me/USMLEWorldStep1

A 45-year-old man is referred to an endocrinologist for newly diagnosed diabetes mellitus. A week ago, his primary care physician noted an elevated fasting serum glucose level. The endocrinologist discusses the different treatment options available, including oral and injectable medications. He recommends treatment with a medication that alters glucose metabolism within the liver by increasing the concentration of fructose 2,6-bisphosphate within hepatocytes. Which of the following conversions will be inhibited by high intracellular concentrations of this metabolite?

- (●) A. Acetyl CoA → fatty acids
- ( ) B. Alanine → glucose
- ( ) C. Fructose-6-phosphate → fructose-1,6-bisphosphate
- ( ) D. Glucose → glycogen
- ( ) E. NAD^+ → NADH

Submit

https://t.me/USMLEWorldStep1

A 45-year-old man is referred to an endocrinologist for newly diagnosed diabetes mellitus. A week ago, his primary care physician noted an elevated fasting serum glucose level. The endocrinologist discusses the different treatment options available, including oral and injectable medications. He recommends treatment with a medication that alters glucose metabolism within the liver by increasing the concentration of fructose 2,6-bisphosphate within hepatocytes. Which of the following conversions will be inhibited by high intracellular concentrations of this metabolite?

- ✗ A. Acetyl CoA → fatty acids (3%)
- ✓ B. Alanine → glucose (37%)
- C. Fructose-6-phosphate → fructose-1,6-bisphosphate (43%)
- D. Glucose → glycogen (10%)
- E. NAD^+ → NADH (5%)

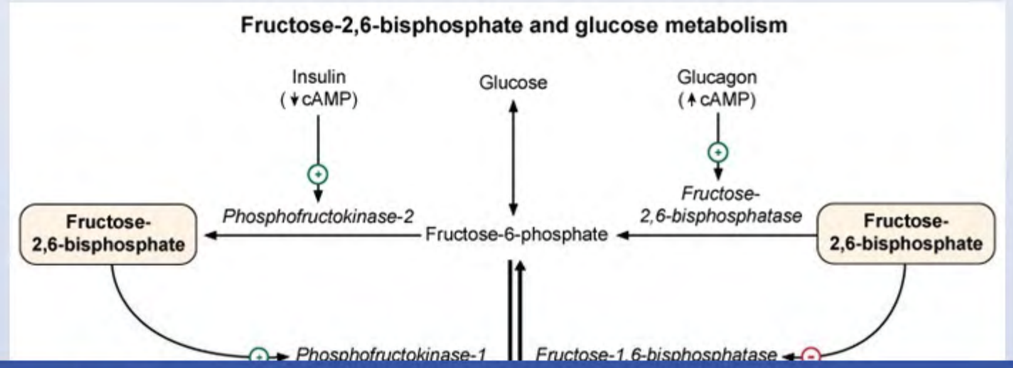
Incorrect
Correct answer
B

37%
Answered correctly

48 secs
Time Spent

2023
Version

Explanation

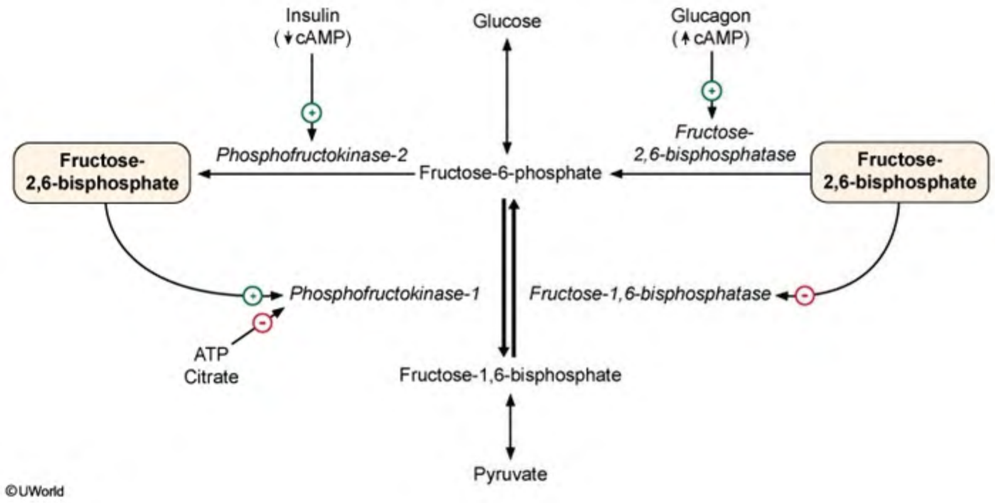


https://t.me/USMLEWorldStep1

A 45-year-old man is referred to an endocrinologist for newly diagnosed diabetes mellitus. A week ago, his primary care p
treatm
medica
bispho
concer

Exhibit Display

Fructose-2,6-bisphosphate and glucose metabolism



©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

©UWorld

Fructose 2,6-bisphosphate helps control the balance between **gluconeogenesis** and **glycolysis** through inverse regulation of phosphofructokinase-1 (PFK-1) and fructose 1,6-bisphosphatase. Fructose 2,6-bisphosphate activates PFK-1, the main regulatory enzyme involved in glycolysis, which converts fructose 6-phosphate to fructose 1,6-bisphosphate. The opposite reaction (fructose 1,6-bisphosphate to fructose-6-phosphate) occurs in gluconeogenesis and is catalyzed by the enzyme fructose-1,6-bisphosphatase (inhibited by fructose 2,6-bisphosphate).

The interconversion of fructose-6-phosphate and fructose 2,6-bisphosphate is achieved by a bifunctional enzyme complex composed of PFK-2 (increases fructose 2,6-bisphosphate levels) and fructose 2,6-bisphosphophosphatase (decreases fructose 2,6-bisphosphate levels). **Insulin** causes activation of PFK-2, leading to **increased fructose 2,6-bisphosphate levels** and **augmented glycolysis**. High concentrations of fructose 2,6-bisphosphate also **inhibit gluconeogenesis**, leading to **decreased conversion of alanine** and other gluconeogenic substrates to glucose.

(Choice A) Fatty acid synthesis is upregulated by insulin and high citrate levels (which increase when acetyl-CoA is abundant, as with active glycolysis). Therefore, fatty acid synthesis is likely to be upregulated in metabolic states in which fructose 2,6-bisphosphate concentration is increased.

(Choice C) The conversion of fructose-6-phosphate to fructose-1,6-bisphosphate is catalyzed by the enzyme PFK-1. This enzyme is allosterically activated by high levels of fructose-2,6-bisphosphate, and so conversion would be increased.

(Choice D) Glycogen formation is stimulated by increased levels of insulin and glucose-6-phosphate. Because elevated insulin levels also increase fructose 2,6-bisphosphate formation, the rise of fructose 2,6-bisphosphate levels in hepatocytes is typically concurrent with increased glycogen synthesis.

(Choice E) The rise in fructose-2,6-bisphosphate accelerates glycolysis, leading to increased conversion of NAD^+ to NADH.

Educational objective:
Fructose 2,6-bisphosphate (F2,6BP) activates phosphofructokinase-1 (increasing glycolysis) and inhibits fructose 1,6-bisphosphatase (decreasing gluconeogenesis). F2,6BP concentration is regulated by a bifunctional enzyme

https://t.me/USMLEWorldStep1

activates PFK-1, the main regulatory enzyme involved in glycolysis, which converts fructose-6-phosphate to fructose 1,6-bisphosphate. The opposite reaction (fructose 1,6-bisphosphate to fructose-6-phosphate) occurs in gluconeogenesis and is catalyzed by the enzyme fructose-1,6-bisphosphatase (inhibited by fructose 2,6-bisphosphate).

The interconversion of fructose-6-phosphate and fructose 2,6-bisphosphate is achieved by a bifunctional enzyme complex composed of PFK-2 (increases fructose 2,6-bisphosphate levels) and fructose 2,6-bisphosphophosphatase (decreases fructose 2,6-bisphosphate levels). **Insulin** causes activation of PFK-2, leading to **increased fructose 2,6-bisphosphate levels** and **augmented glycolysis**. High concentrations of fructose 2,6-bisphosphate also **inhibit gluconeogenesis**, leading to **decreased conversion of alanine** and other gluconeogenic substrates to glucose.

(Choice A) Fatty acid synthesis is upregulated by insulin and high citrate levels (which increase when acetyl-CoA is abundant, as with active glycolysis). Therefore, fatty acid synthesis is likely to be upregulated in metabolic states in which fructose 2,6-bisphosphate concentration is increased.

(Choice C) The conversion of fructose-6-phosphate to fructose-1,6-bisphosphate is catalyzed by the enzyme PFK-1. This enzyme is allosterically activated by high levels of fructose-2,6-bisphosphate, and so conversion would be increased.

(Choice D) Glycogen formation is stimulated by increased levels of insulin and glucose-6-phosphate. Because elevated insulin levels also increase fructose 2,6-bisphosphate formation, the rise of fructose 2,6-bisphosphate levels in hepatocytes is typically concurrent with increased glycogen synthesis.

(Choice E) The rise in fructose-2,6-bisphosphate accelerates glycolysis, leading to increased conversion of NAD^+ to NADH.

Educational objective:
Fructose 2,6-bisphosphate (F2,6BP) activates phosphofructokinase-1 (increasing glycolysis) and inhibits fructose 1,6-bisphosphatase (decreasing gluconeogenesis). F2,6BP concentration is regulated by a bifunctional enzyme complex: phosphofructokinase-2 increases F2,6BP levels in response to insulin, and fructose 2,6-bisphosphatase decreases F2,6BP levels in response to glucagon.

References

https://t.me/USMLEWorldStep1

A 20-year-old woman with cystic fibrosis comes to the clinic for routine follow-up. She has no concerns since her last visit 3 months ago. Vital signs are normal. Examination shows a hyperexpanded chest with equal aeration bilaterally. Fasting glucose level is 90 mg/dL. Plasma glucose level 2 hours after oral glucose tolerance testing is 185 mg/dL (normal: <140). Which of the following is the primary mechanism responsible for this patient's abnormal test result?

- A. Decreased insulin production due to disruption of pancreatic islet cells
- B. Decreased insulin production due to pancreatic islet cell autoantibodies
- C. Increased glucagon secretion due to chronic malnutrition
- D. Increased insulin degradation due to hypermetabolic needs
- E. Increased insulin resistance from chronic stimulation by cortisol and epinephrine

Submit

https://t.me/USMLEWorldStep1

A 20-year-old woman with cystic fibrosis comes to the clinic for routine follow-up. She has no concerns since her last visit 3 months ago. Vital signs are normal. Examination shows a hyperexpanded chest with equal aeration bilaterally. Fasting glucose level is 90 mg/dL. Plasma glucose level 2 hours after oral glucose tolerance testing is 185 mg/dL (normal: <140). Which of the following is the primary mechanism responsible for this patient's abnormal test result?

- ✓ A. Decreased insulin production due to disruption of pancreatic islet cells (81%)
- B. Decreased insulin production due to pancreatic islet cell autoantibodies (4%)
- C. Increased glucagon secretion due to chronic malnutrition (5%)
- D. Increased insulin degradation due to hypermetabolic needs (2%)
- E. Increased insulin resistance from chronic stimulation by cortisol and epinephrine (7%)

Correct | 81% Answered correctly | 03 secs Time Spent | 2023 Version

Explanation

Cystic fibrosis (CF) is an autosomal recessive disorder caused by a mutation (eg, ΔF508) in the gene encoding the CF transmembrane conductance regulator (CFTR) protein. CFTR normally regulates the transport of chloride ions across secretory epithelial cells; a defect in this protein leads to the accumulation of **thick, inspissated secretions** in ducts throughout the body (eg, lungs, pancreas, gastrointestinal tract, vas deferens).

In the pancreas, dehydrated, viscous secretions block the lumen of the **pancreatic ducts**, causing both **exocrine** (ie, malabsorption) and **endocrine dysfunction**. Endocrine dysfunction is due to pancreatic fibrosis and fat infiltration, which cause progressive encroachment, disruption, and **destruction of pancreatic islet cells**. This injury results in **decreased insulin production** and **CF-related diabetes** (CFRD). In the initial stages, glucose is typically normal when fasting (ie, able to produce some insulin) but elevated after a glycemic load, as seen in this

https://t.me/USMLEWorldStep1

Explanation

Cystic fibrosis (CF) is an autosomal recessive disorder caused by a mutation (eg, ΔF508) in the gene encoding the CF transmembrane conductance regulator (CFTR) protein. CFTR normally regulates the transport of chloride ions across secretory epithelial cells; a defect in this protein leads to the accumulation of **thick, inspissated secretions** in ducts throughout the body (eg, lungs, pancreas, gastrointestinal tract, vas deferens).

In the pancreas, dehydrated, viscous secretions block the lumen of the **pancreatic ducts**, causing both **exocrine** (ie, malabsorption) and **endocrine dysfunction**. Endocrine dysfunction is due to pancreatic fibrosis and fat infiltration, which cause progressive encroachment, disruption, and **destruction of pancreatic islet cells**. This injury results in **decreased insulin production** and **CF-related diabetes** (CFRD). In the initial stages, glucose is typically normal when fasting (ie, able to produce some insulin) but elevated after a glycemic load, as seen in this patient. As the disease progresses, there is fasting hyperglycemia and increasing hemoglobin A1c levels.

Because early diagnosis and treatment with insulin are associated with improved pulmonary status and overall survival, all CF patients should undergo regular screening with oral glucose tolerance tests.

(Choice B) Decreased insulin production due to pancreatic islet cell autoantibodies describes the pathogenesis of type 1 diabetes mellitus. Islet cell destruction in CFRD is not an autoimmune process.

(Choice C) Although glucagon increases in response to starvation, chronic malnutrition is likely to result in glucagon resistance. In addition, glucagon-producing alpha islet cells are damaged along with beta cells in patients with CF, resulting in decreased glucagon secretion.

(Choices D and E) Stress-induced hyperglycemia and insulin resistance can occur in times of acutely increased metabolic demand (eg, trauma, burn, sepsis) due to the release of cortisol, epinephrine, and glucagon. Patients with late-stage CFRD may have a component of insulin resistance during times of acute stress and inflammation (eg, pulmonary exacerbation); however, this is not the primary mechanism of CFRD.

Educational objective:
Cystic fibrosis (CF) causes the accumulation of thick, viscous secretions in ducts throughout the body. CF-related diabetes occurs after the progressive destruction of pancreatic islet cells leads to decreased insulin production.

https://t.me/USMLEWorldStep1

CF transmembrane conductance regulator (CFTR) protein. CFTR normally regulates the transport of chloride ions across secretory epithelial cells; a defect in this protein leads to the accumulation of **thick, inspissated secretions** in ducts throughout the body (eg, lungs, pancreas, gastrointestinal tract, vas deferens).

In the pancreas, dehydrated, viscous secretions block the lumen of the **pancreatic ducts**, causing both **exocrine** (ie, malabsorption) and **endocrine dysfunction**. Endocrine dysfunction is due to pancreatic fibrosis and fat infiltration, which cause progressive encroachment, disruption, and **destruction of pancreatic islet cells**. This injury results in **decreased insulin production** and **CF-related diabetes** (CFRD). In the initial stages, glucose is typically normal when fasting (ie, able to produce some insulin) but elevated after a glycemic load, as seen in this patient. As the disease progresses, there is fasting hyperglycemia and increasing hemoglobin A1c levels.

Because early diagnosis and treatment with insulin are associated with improved pulmonary status and overall survival, all CF patients should undergo regular screening with oral glucose tolerance tests.

(Choice B) Decreased insulin production due to pancreatic islet cell autoantibodies describes the pathogenesis of type 1 diabetes mellitus. Islet cell destruction in CFRD is not an autoimmune process.

(Choice C) Although glucagon increases in response to starvation, chronic malnutrition is likely to result in glucagon resistance. In addition, glucagon-producing alpha islet cells are damaged along with beta cells in patients with CF, resulting in decreased glucagon secretion.

(Choices D and E) Stress-induced hyperglycemia and insulin resistance can occur in times of acutely increased metabolic demand (eg, trauma, burn, sepsis) due to the release of cortisol, epinephrine, and glucagon. Patients with late-stage CFRD may have a component of insulin resistance during times of acute stress and inflammation (eg, pulmonary exacerbation); however, this is not the primary mechanism of CFRD.

Educational objective:
Cystic fibrosis (CF) causes the accumulation of thick, viscous secretions in ducts throughout the body. CF-related diabetes occurs after the progressive destruction of pancreatic islet cells leads to decreased insulin production.

References

- Cystic fibrosis related diabetes: pathophysiology, screening and diagnosis.

https://t.me/USMLEWorldStep1

Exhibit Display

Features of cystic fibrosis	
Pathogenesis	• Autosomal recessive mutation (**ΔF508**) impairs CFTR function • Decreased water content causes **thick, viscous mucus**: ◦ Chronic airway obstruction ◦ Gastrointestinal malabsorption
Clinical manifestations	• Chronic, productive cough • Recurrent **sinopulmonary infections** (eg, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, & *Burkholderia cepacia* complex) • **Pancreatic insufficiency** • Male infertility (bilateral absence of vas deferens)
Diagnosis	• Elevated sweat chloride levels • Nasal potential difference measurements • Genetic testing for *CFTR* mutations
CFTR = cystic fibrosis transmembrane conductance regulator.	

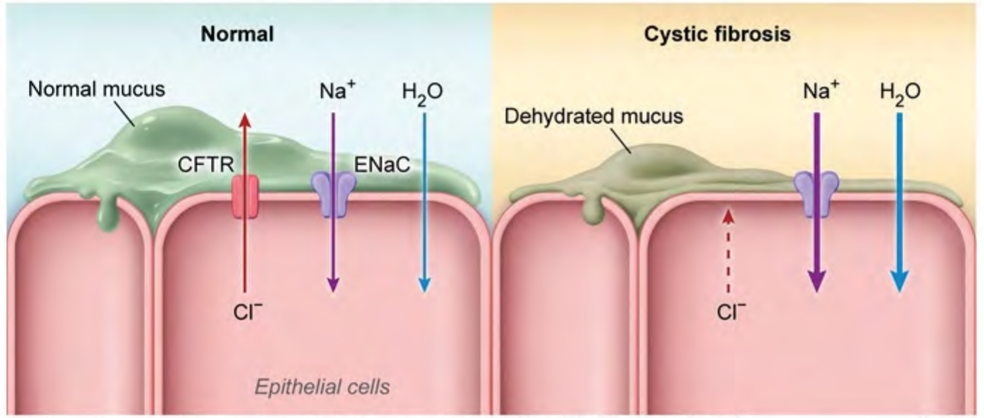
New | Existing | My Notebook

(eg, pulmonary exacerbation); however, this is not the primary mechanism of CFRD.

https://t.me/USMLEWorldStep1

Exhibit Display

Respiratory mucosa



CFTR = cystic fibrosis transmembrane conductance regulator; **ENaC** = epithelial sodium channel. ©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Cystic
CF tra
across
in duct

In the
(ie, ma
infiltrat
injury
typical
patient

Becau
surviva

(Choi
type 1

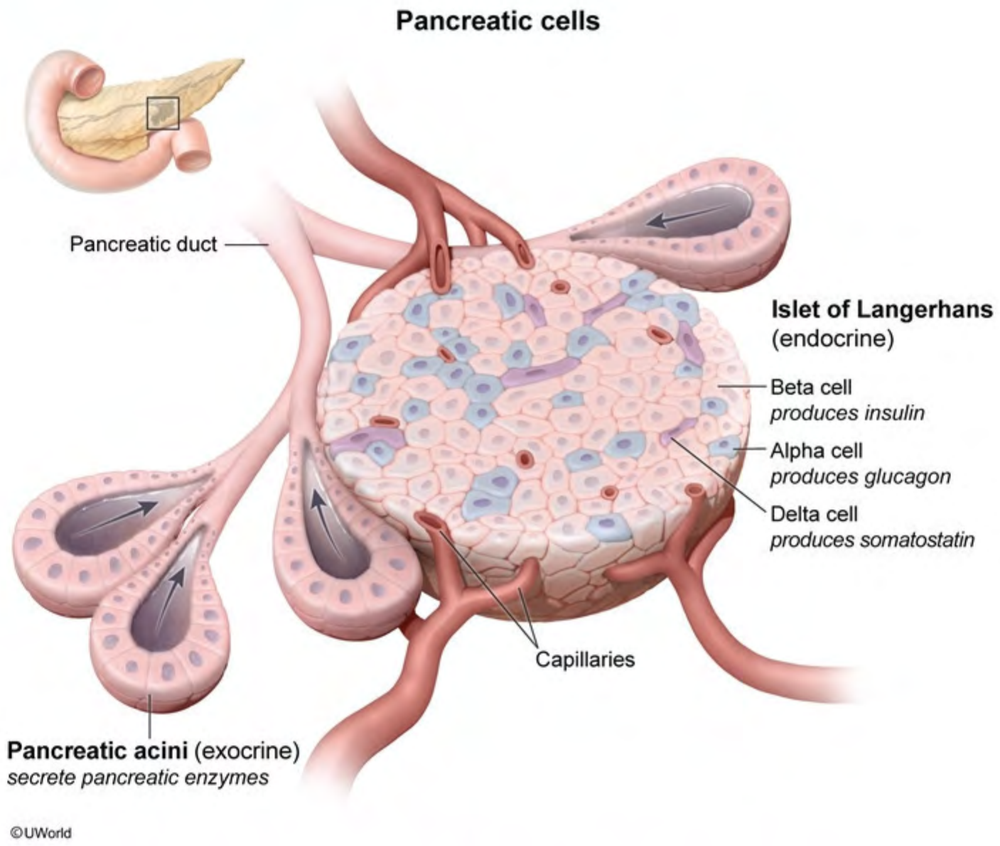
(Choi
glucag
patient

(Choi
metabolic demand (eg, trauma, burn, sepsis) due to the release of cortisol, epinephrine, and glucagon. Patients with late-stage CFRD may have a component of insulin resistance during times of acute stress and inflammation (eg, pulmonary exacerbation); however, this is not the primary mechanism of CFRD.

https://t.me/USMLEWorldStep1

Cor 81% 03 secs 2023

Exhibit Display



Zoom In Zoom Out Reset New | Existing My Notebook

Expl

Cystic
CF tra
across
in duct

In the
(ie, ma
infiltrat
injury
typical
patien

Becau
surviva

(Choi
type 1

(Choi
glucag
patien

(Choi
metab
with la
(eg, pulmonary exacerbation); however, this is not the primary mechanism of CFRD.

https://t.me/USMLEWorldStep1

A 7-year-old boy is being evaluated for growth retardation. Brain MRI shows a 4 cm multiloculated, cystic, suprasellar lesion, which is bulging into the floor of the third ventricle and base of the brain. Calcifications are present. From which of the following structures is this mass most likely derived?

- A. Prolactin secreting cells of the anterior pituitary
- B. Remnants of the Rathke pouch
- C. Astrocytes
- D. Arachnoid cap cells
- E. Posterior pituitary cells

Submit

https://t.me/USMLEWorldStep1

A 7-year-old boy is being evaluated for growth retardation. Brain MRI shows a 4 cm multiloculated, cystic, suprasellar lesion, which is bulging into the floor of the third ventricle and base of the brain. Calcifications are present. From which of the following structures is this mass most likely derived?

- ✗ A. Prolactin secreting cells of the anterior pituitary (6%)
- ✓ B. Remnants of the Rathke pouch (80%)
- C. Astrocytes (7%)
- D. Arachnoid cap cells (2%)
- E. Posterior pituitary cells (3%)

Incorrect
Correct answer
B

80%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

Craniopharyngiomas are tumors arising from remnants of Rathke's pouch. The anterior pituitary is formed from an out-pouching of the pharyngeal roof and is called Rathke's pouch. The posterior pituitary gland arises from an extension of the hypothalamic neurons. Together, the anterior and posterior pituitary glands lie in the sella turcica at the skull base.

During the time of pituitary development, remnants of Rathke's pouch cells can remain in the diencephalon (the posterior region of the forebrain). Neoplastic transformation of these "pouch cells" is called a craniopharyngioma. Typically, craniopharyngiomas have three components: solid, comprised of the actual tumor cells; cystic, filled with "machinery oil" liquid; and a calcified component. Any suprasellar mass with three components is highly suggestive of craniopharyngioma. Craniopharyngioma symptoms include headaches, visual field defects, and hypopituitarism, evidenced by the growth retardation of this child. Ultimately, compression of the pituitary stalk by craniopharyngioma leads to hyperprolactinemia by loss of dopaminergic inhibition. Craniopharyngiomas are

https://t.me/USMLEWorldStep1

Craniopharyngiomas are tumors arising from remnants of Rathke's pouch. The anterior pituitary is formed from an out-pouching of the pharyngeal roof and is called Rathke's pouch. The posterior pituitary gland arises from an extension of the hypothalamic neurons. Together, the anterior and posterior pituitary glands lie in the sella turcica at the skull base.

During the time of pituitary development, remnants of Rathke's pouch cells can remain in the diencephalon (the posterior region of the forebrain). Neoplastic transformation of these "pouch cells" is called a craniopharyngioma. Typically, craniopharyngiomas have three components: solid, comprised of the actual tumor cells; cystic, filled with "machinery oil" liquid; and a calcified component. Any suprasellar mass with three components is highly suggestive of craniopharyngioma. Craniopharyngioma symptoms include headaches, visual field defects, and hypopituitarism, evidenced by the growth retardation of this child. Ultimately, compression of the pituitary stalk by craniopharyngioma leads to hyperprolactinemia by loss of dopaminergic inhibition. Craniopharyngiomas are usually tumors of childhood, being most frequently discovered between the ages of 5 and 10 years of age.

(Choice A) Prolactinomas are uncommon in young children. They typically appear as a homogenous mass when imaged.

(Choice C) Gliomas can occur in the suprasellar region if they arise from the optic apparatus, but do not appear on imaging with the three components described above. Gliomas typically presents with visual symptoms, hypothalamic dysfunction, and hypopituitarism.

(Choice D) Meningiomas are tumors of the leptomeninges, which is the lining of the brain. Hence, meningiomas can occur in any "lined" part of the brain including sellar and suprasellar regions. Meningiomas are usually homogeneous appearance on MRI and can be seen "sticking" to leptomeninges.

Educational Objective:

1. The anterior pituitary is formed from an out-pouching of the pharyngeal roof and is called Rathke's pouch. The posterior pituitary gland arises from an extension of the hypothalamic neurons.
2. Craniopharyngiomas are tumors arising from Rathke's pouch remnants in the anterior pituitary. They characteristically have three components: solid, cystic, and calcified. They present during childhood, usually, with mass effect and visual deficits.

https://t.me/USMLEWorldStep1

A 53-year-old man comes to the office due to uncontrolled type 2 diabetes mellitus. The patient was diagnosed 3 years ago and prescribed metformin and lifestyle modification. In the past year, his hemoglobin A1c levels have been steadily rising. Blood pressure is 145/90 mm Hg. BMI is 37 kg/m^2. Laboratory results are normal except for a fasting plasma glucose of 155 mg/dL and a hemoglobin A1c level of 8%. Additional treatment with canagliflozin is initiated. Over the next several days, which of the following effects are most likely to occur in this patient due to the new medication?

	Urinary glucose excretion	Total body sodium content	Extracellular fluid volume
○ A.	Decreased	Decreased	Unchanged
○ B.	Decreased	Increased	Decreased
○ C.	Increased	Decreased	Decreased
○ D.	Increased	Unchanged	Increased
○ E.	Increased	Increased	Decreased

Submit

https://t.me/USMLEWorldStep1

A 53-year-old man comes to the office due to uncontrolled type 2 diabetes mellitus. The patient was diagnosed 3 years ago and prescribed metformin and lifestyle modification. In the past year, his hemoglobin A1c levels have been steadily rising. Blood pressure is 145/90 mm Hg. BMI is 37 kg/m^2. Laboratory results are normal except for a fasting plasma glucose of 155 mg/dL and a hemoglobin A1c level of 8%. Additional treatment with canagliflozin is initiated. Over the next several days, which of the following effects are most likely to occur in this patient due to the new medication?

	Urinary glucose excretion	Total body sodium content	Extracellular fluid volume	
✗ A.	Decreased	Decreased	Unchanged	(1%)
B.	Decreased	Increased	Decreased	(1%)
✓ C.	Increased	Decreased	Decreased	(70%)
D.	Increased	Unchanged	Increased	(9%)
E.	Increased	Increased	Decreased	(16%)

Incorrect
Correct answer
C

70%
Answered correctly

03 secs
Time Spent

2023
Version

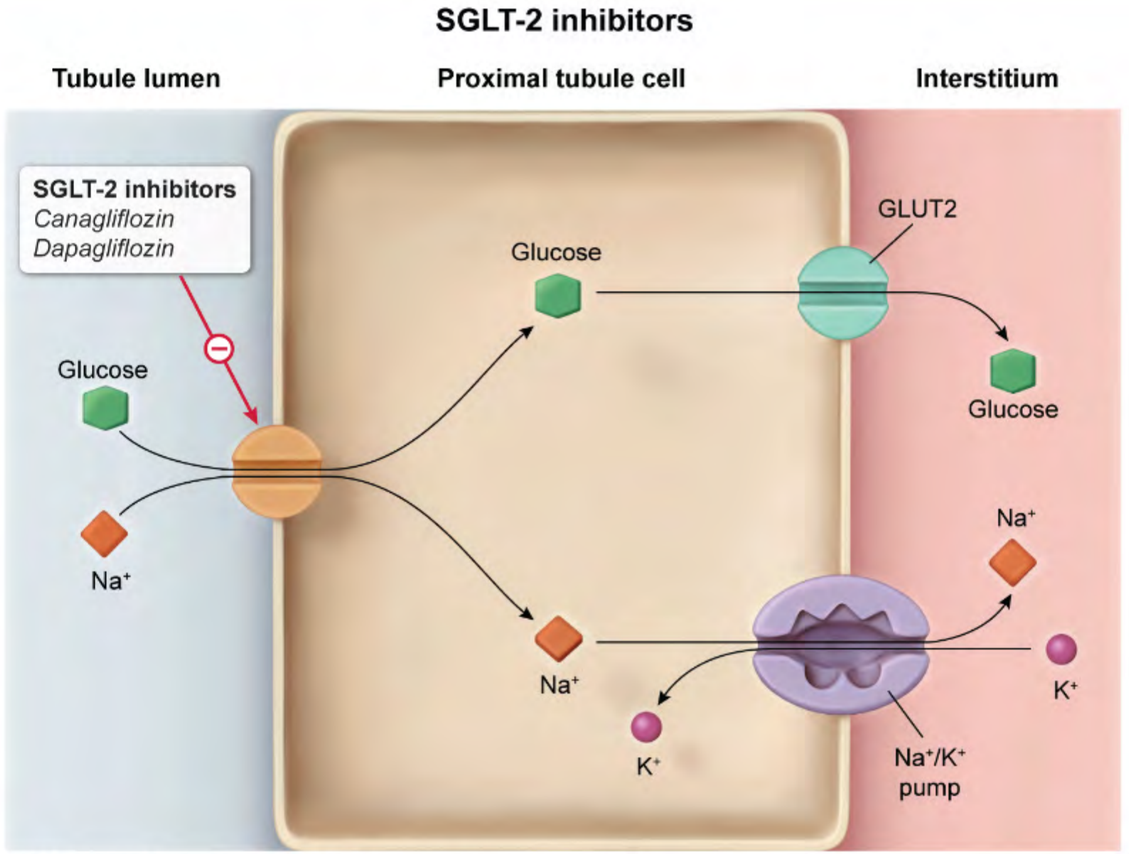
Explanation



https://t.me/USMLEWorldStep1

A 53-year-old man comes to the office due to uncontrolled type 2 diabetes mellitus. The patient was diagnosed 3 years
been s
a fasti
is initia
the ne

Exhibit Display

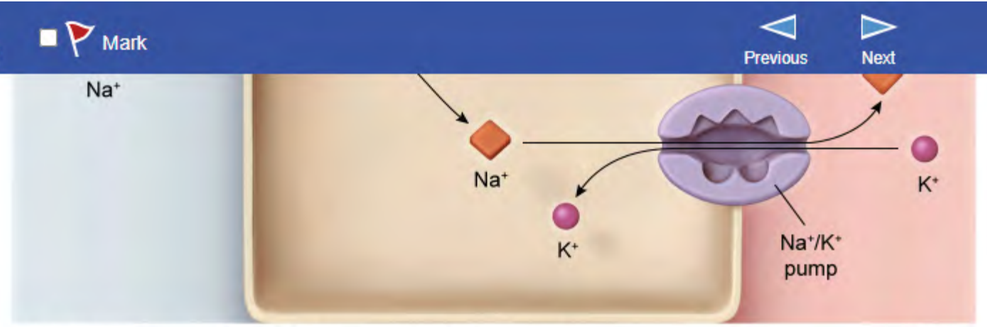


GLUT2 = glucose transporter 2; **SGLT-2** = sodium-glucose cotransporter 2.

©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1



GLUT2 = glucose transporter 2; **SGLT-2** = sodium-glucose cotransporter 2. ©UWorld

Sodium-glucose cotransporter 2 (SGLT2) is a low-affinity, high-capacity transport protein that normally reabsorbs 90% of filtered glucose in the proximal renal tubule. Glucose reabsorption by SGLT2 is driven by the cotransport of sodium, which occurs down its concentration gradient. The sodium is actively pumped across the basolateral membrane by Na-K-ATPase, and glucose follows by facilitated diffusion via glucose transporter 2.

SGLT2 inhibitors (eg, canagliflozin, dapagliflozin) are oral antidiabetic agents that have the following effects:

- Decreased renal reabsorption of glucose, leading to **increased urinary glucose excretion** and lower blood glucose levels
- Natriuresis and osmotic **diuresis** due to decreased reabsorption of sodium and glucose, leading to a small **decrease in extracellular fluid volume**, total **body sodium content**, and blood pressure
- Decreased sodium reabsorption and increased tubular sodium delivery to the macula densa, leading to decreased activation of the renin-angiotensin-aldosterone system, lower glomerular (and systemic) pressure, and delayed progression of nephropathy

Educational objective:
Sodium-glucose cotransporter 2 inhibitors decrease renal reabsorption of glucose and sodium, leading to increased urinary glucose excretion and decreased blood glucose levels. In addition, natriuresis and osmotic diuresis lead to a small decrease in extracellular fluid volume, total body sodium content, and blood pressure.

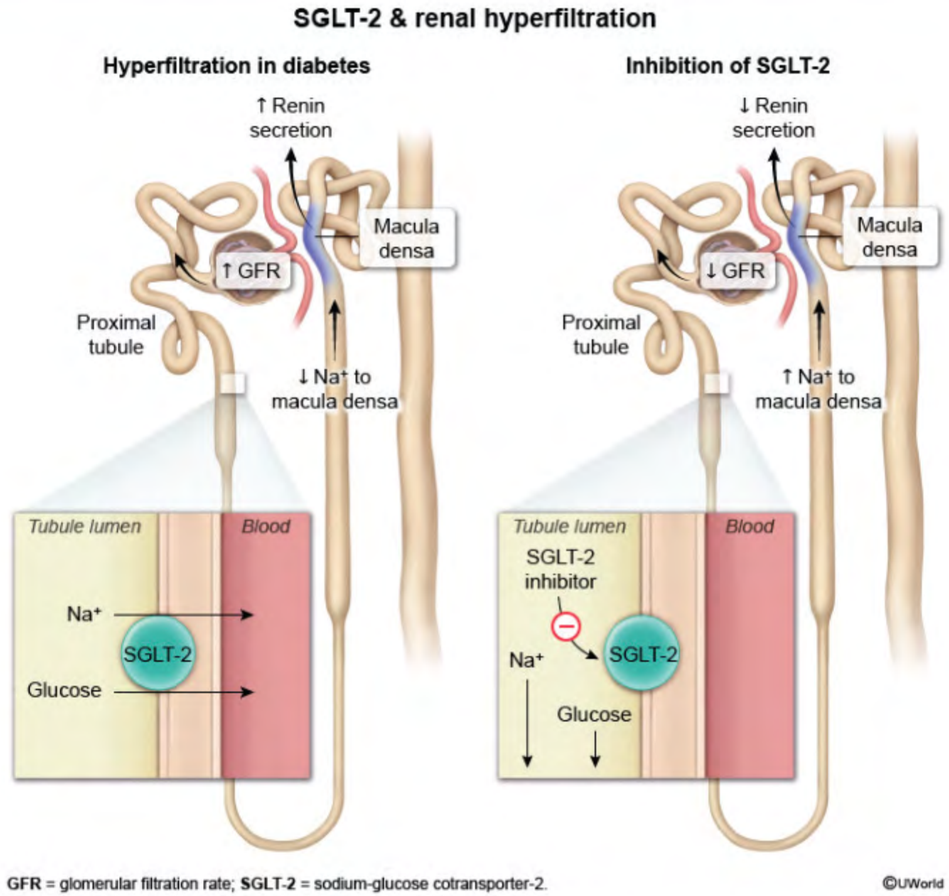
Pharmacology	Endocrine, Diabetes & Metabolism	Diabetes mellitus
Subject	System	Topic

Copyright © UWorld. All rights reserved.

https://t.me/USMLEWorldStep1

Na⁺

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Sodiu
90% o
sodiu
memb

SGLT

- D
g
- N
d
- D
d
a

Educa
Sodiu
increa
diures

Pharma
Subject

Copyright © UWorld. All rights reserved.

https://t.me/USMLEWorldStep1

A 27-year-old woman comes to the office for evaluation of infertility. The patient and her husband have been trying to conceive for the past 2 years but have been unsuccessful. Her husband recently underwent infertility evaluation and was found to have no abnormalities. The patient's menses began at age 13, and her menstrual cycles were regular until the last few years, when they began occurring at intervals of 3-4 months. She has occasional headaches but no other symptoms. The patient has no prior medical conditions and takes no medications. On physical examination, the patient appears normal and has well-developed secondary sexual characteristics. Cardiopulmonary and abdominal examinations are normal. Pelvic examination reveals no adnexal masses. Neurological examination shows diminished vision in the bilateral temporal visual fields. Examination of the other cranial nerves is normal and there is no focal weakness or sensory loss. An abnormality originating in which of the following is the most likely cause of this patient's current condition?

- A. Hypothalamic neurons
- B. Ovarian granulosa cells
- C. Ovarian theca cells
- D. Pituitary lactotrophs
- E. Pituitary somatotrophs

Submit

https://t.me/USMLEWorldStep1

A 27-year-old woman comes to the office for evaluation of infertility. The patient and her husband have been trying to conceive for the past 2 years but have been unsuccessful. Her husband recently underwent infertility evaluation and was found to have no abnormalities. The patient's menses began at age 13, and her menstrual cycles were regular until the last few years, when they began occurring at intervals of 3-4 months. She has occasional headaches but no other symptoms. The patient has no prior medical conditions and takes no medications. On physical examination, the patient appears normal and has well-developed secondary sexual characteristics. Cardiopulmonary and abdominal examinations are normal. Pelvic examination reveals no adnexal masses. Neurological examination shows diminished vision in the bilateral temporal visual fields. Examination of the other cranial nerves is normal and there is no focal weakness or sensory loss. An abnormality originating in which of the following is the most likely cause of this patient's current condition?

- A. Hypothalamic neurons
- B. Ovarian granulosa cells
- C. Ovarian theca cells
- D. Pituitary lactotrophs
- E. Pituitary somatotrophs

Submit

https://t.me/USMLEWorldStep1

A 27-year-old woman comes to the office for evaluation of infertility. The patient and her husband have been trying to conceive for the past 2 years but have been unsuccessful. Her husband recently underwent infertility evaluation and was found to have no abnormalities. The patient's menses began at age 13, and her menstrual cycles were regular until the last few years, when they began occurring at intervals of 3-4 months. She has occasional headaches but no other symptoms. The patient has no prior medical conditions and takes no medications. On physical examination, the patient appears normal and has well-developed secondary sexual characteristics. Cardiopulmonary and abdominal examinations are normal. Pelvic examination reveals no adnexal masses. Neurological examination shows diminished vision in the bilateral temporal visual fields. Examination of the other cranial nerves is normal and there is no focal weakness or sensory loss. An abnormality originating in which of the following is the most likely cause of this patient's current condition?

- A. Hypothalamic neurons (3%)
- ✗ B. Ovarian granulosa cells (0%)
- C. Ovarian theca cells (1%)
- ✓ D. Pituitary lactotrophs (85%)
- E. Pituitary somatotrophs (8%)

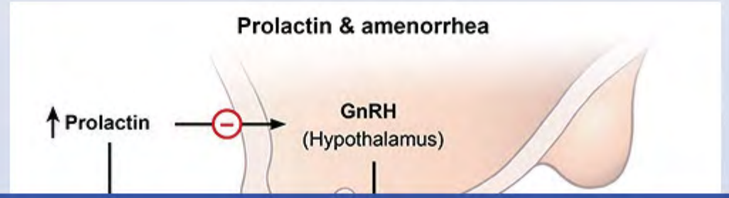
Incorrect
Correct answer
D

85%
Answered correctly

09 secs
Time Spent

2023
Version

Explanation



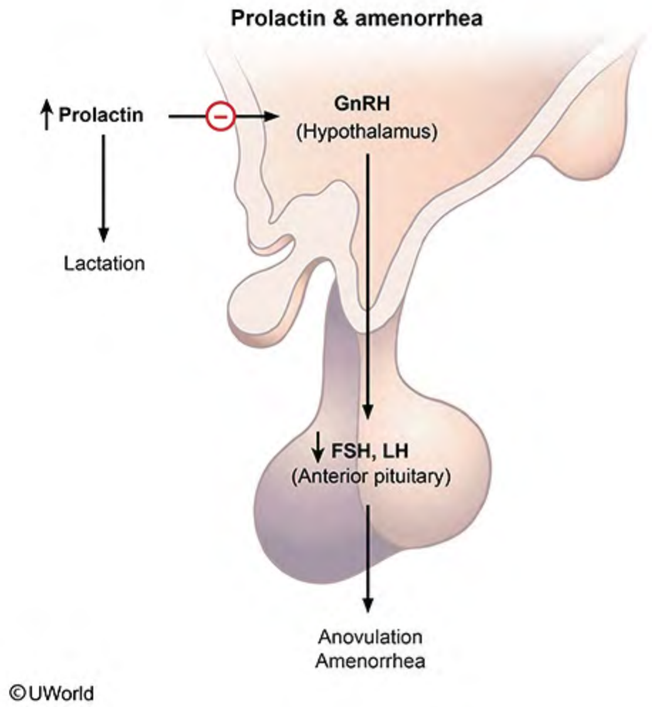
https://t.me/USMLEWorldStep1

E. Pituitary somatotrophs (8%)

Inco
Corre
D

Expl

Exhibit Display



Zoom In Zoom Out Reset New | Existing My Notebook

This p
to mas
hemia

The most common type of pituitary adenoma is a **prolactinoma**. Prolactin is a peptide hormone secreted from

https://t.me/USMLEWorldStep1

©UWorld

This patient's symptoms are concerning for a **pituitary tumor**. Large pituitary tumors can cause **headaches** due to mass effect, and compression of the optic chiasm by suprasellar extension of the tumor can lead to bitemporal hemianopsia.

The most common type of pituitary adenoma is a **prolactinoma**. Prolactin is a peptide hormone secreted from lactotrophs of the pituitary gland whose primary physiologic action is maintenance of lactation in postpartum women. Hyperprolactinemia also **suppresses GnRH production** in the hypothalamus, leading to **oligomenorrhea/amenorrhea** and infertility. Suppression of ovulation is also seen as a physiologic effect of breastfeeding, which supports elevated prolactin levels for 6 months or more postpartum.

(Choice A) Kallmann syndrome is a disorder involving the GnRH-producing neurons in the hypothalamus. In addition to decreased sense of smell (anosmia/hyposomia), this condition causes hypogonadotropic hypogonadism and presents with short stature and delayed puberty (primary amenorrhea). This patient has secondary amenorrhea (ie, normal initial onset of puberty followed by menstrual dysregulation), and her bilateral temporal visual deficits are more suggestive of a pituitary rather than hypothalamic lesion.

(Choice B) Ovarian granulosa cells produce estrogen, progesterone, and inhibin. Loss of these cells (eg, due to autoimmune disorder) can lead to primary ovarian insufficiency and present with infertility and secondary amenorrhea. However, patients often have hypoestrogenic symptoms (eg, hot flashes), and this disorder would not cause visual field defects.

(Choice C) Ovarian theca cells produce androgens, which provide the substrate for subsequent synthesis of estrogens. Amenorrhea and infertility related to hyperactivity of these cells are typically associated with signs of hyperandrogenism (eg, hirsutism).

(Choice E) Unlike most pituitary hormones, which are under positive regulation by the hypothalamus, prolactin is primarily under negative regulation by hypothalamic dopaminergic neurons via the pituitary stalk. Because of this, any pituitary tumor of significant size that disrupts these dopaminergic pathways can cause moderate hyperprolactinemia. However, somatotroph adenomas typically cause acromegaly, with prognathism and bony enlargement of the hands and feet.

Educational objective:

https://t.me/USMLEWorldStep1

©UWorld

This p... to mas... hemia...

The m... lactotr... wome... **oligon**... breast...

(Choi... additic... hypog... secon... tempo...

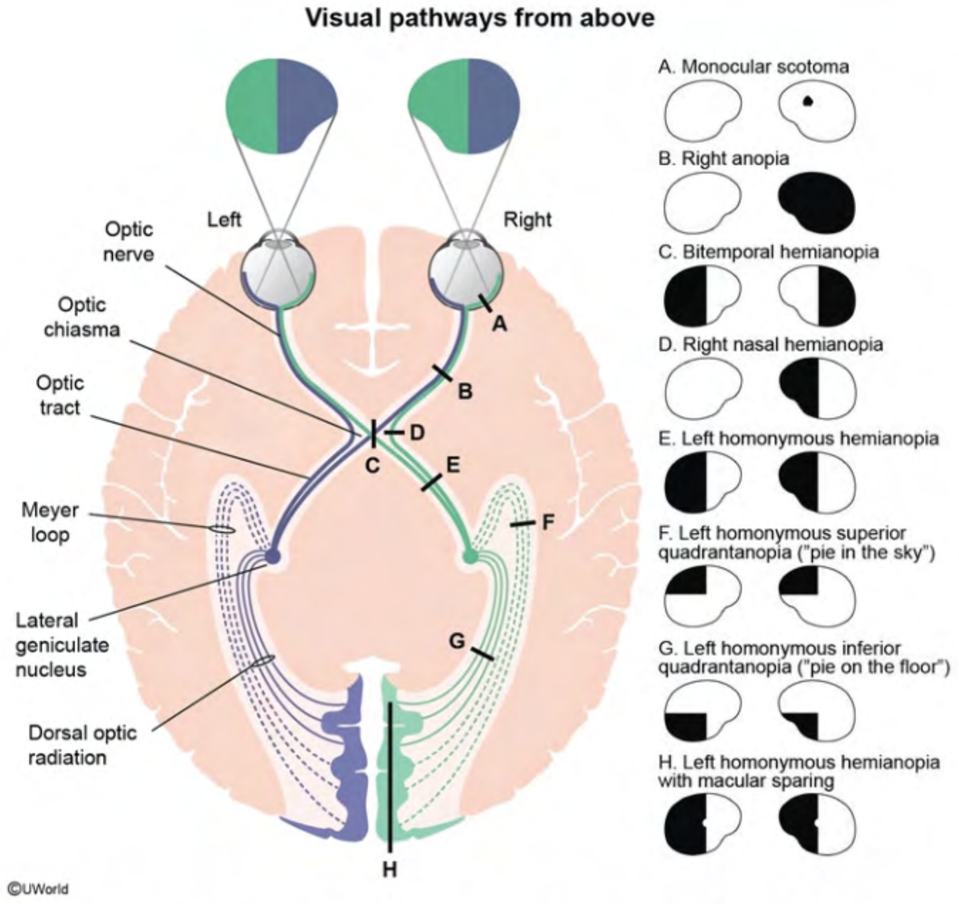
(Choi... autoim... amenc... not ca...

(Choi... estrog... hypera...

(Choi... primar... any pi... hyperp... enlargement of the hands and feet.

Educational objective:

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

women. Hyperprolactinemia also **suppresses GnRH production** in the hypothalamus, leading to **oligomenorrhea/amenorrhea** and infertility. Suppression of ovulation is also seen as a physiologic effect of breast

(Choi
additio
hypog
secon
tempo

(Choi
autoim
amen
not ca

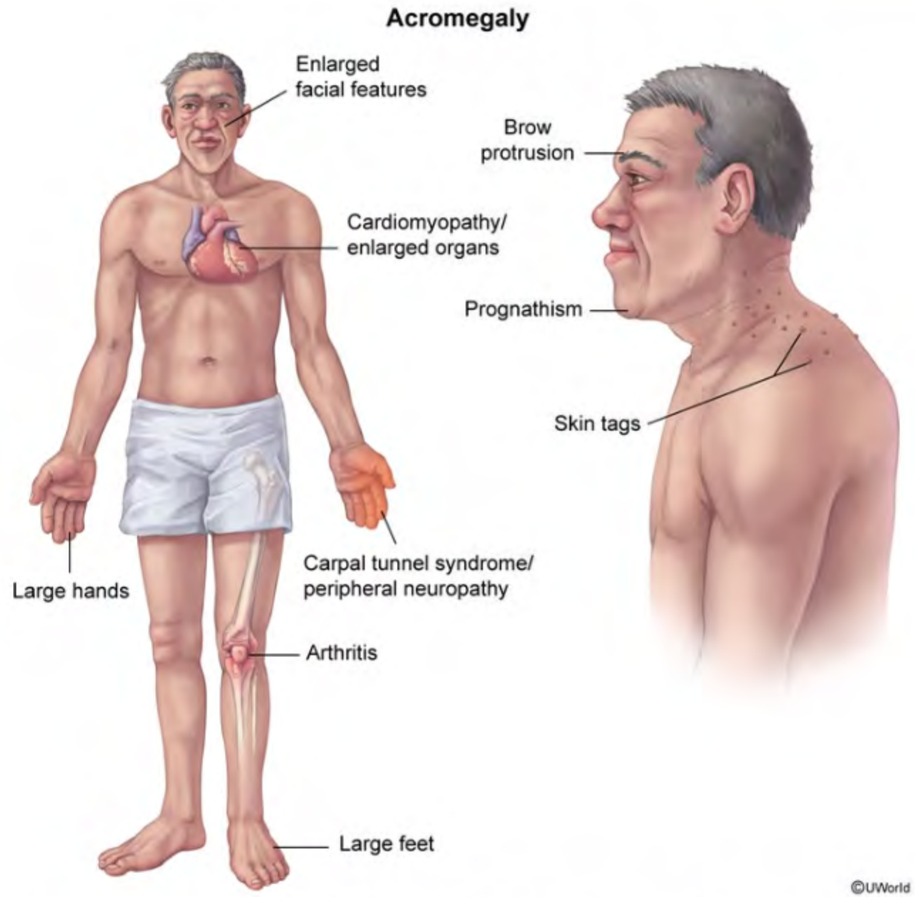
(Choi
estrog
hypera

(Choi
primar
any pi
hyperp
enlarg

Educa
Prolac
infertili
bitemp

Refere
- Progress in the diagnosis and classification of pituitary adenomas.

Exhibit Display



Zoom In Zoom Out Reset New | Existing My Notebook

https://t.me/USMLEWorldStep1

A 56-year-old man with type 2 diabetes mellitus, hypertension, and hyperlipidemia comes to the office due to elevated blood glucose levels. The patient's current medications include metformin, lisinopril, and simvastatin. Blood pressure is 150/90 mm Hg and pulse is 88/min. BMI is 37 kg/m^2. Physical examination is unremarkable. Laboratory studies show a fasting glucose level of 156 mg/dL, serum creatinine of 1.1 mg/dL, hemoglobin A1c of 8.1%, and urine albumin-creatinine ratio of 200 mg/g (normal: <30). Treatment with empagliflozin is initiated. Which of the following effects is most likely to be seen with this new treatment?

- A. Decreased intestinal glucose absorption
- B. Increased body weight
- C. Increased endogenous insulin production
- D. Reduction in glomerular hyperfiltration
- E. Suppression of glucagon secretion

Submit

https://t.me/USMLEWorldStep1

A 56-year-old man with type 2 diabetes mellitus, hypertension, and hyperlipidemia comes to the office due to elevated blood glucose levels. The patient's current medications include metformin, lisinopril, and simvastatin. Blood pressure is 150/90 mm Hg and pulse is 88/min. BMI is 37 kg/m^2. Physical examination is unremarkable. Laboratory studies show a fasting glucose level of 156 mg/dL, serum creatinine of 1.1 mg/dL, hemoglobin A1c of 8.1%, and urine albumin-creatinine ratio of 200 mg/g (normal: <30). Treatment with empagliflozin is initiated. Which of the following effects is most likely to be seen with this new treatment?

- A. Decreased intestinal glucose absorption (22%)
- ✗ B. Increased body weight (7%)
- C. Increased endogenous insulin production (8%)
- ✓ D. Reduction in glomerular hyperfiltration (54%)
- E. Suppression of glucagon secretion (6%)

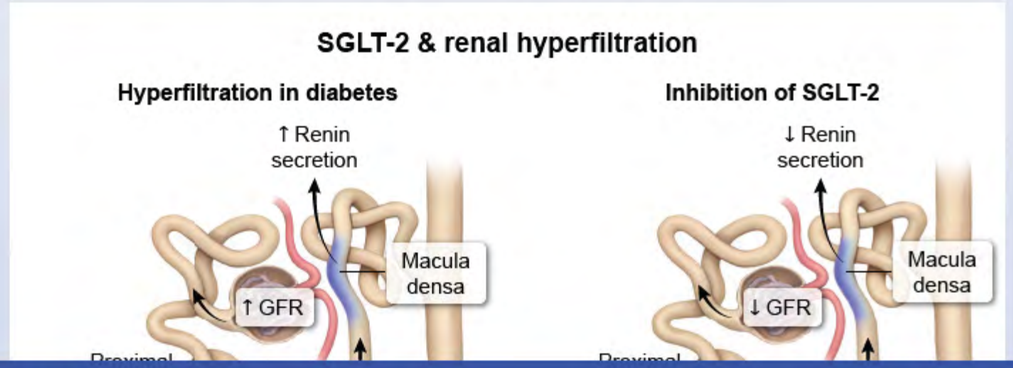
Incorrect
Correct answer
D

54%
Answered correctly

04 secs
Time Spent

2023
Version

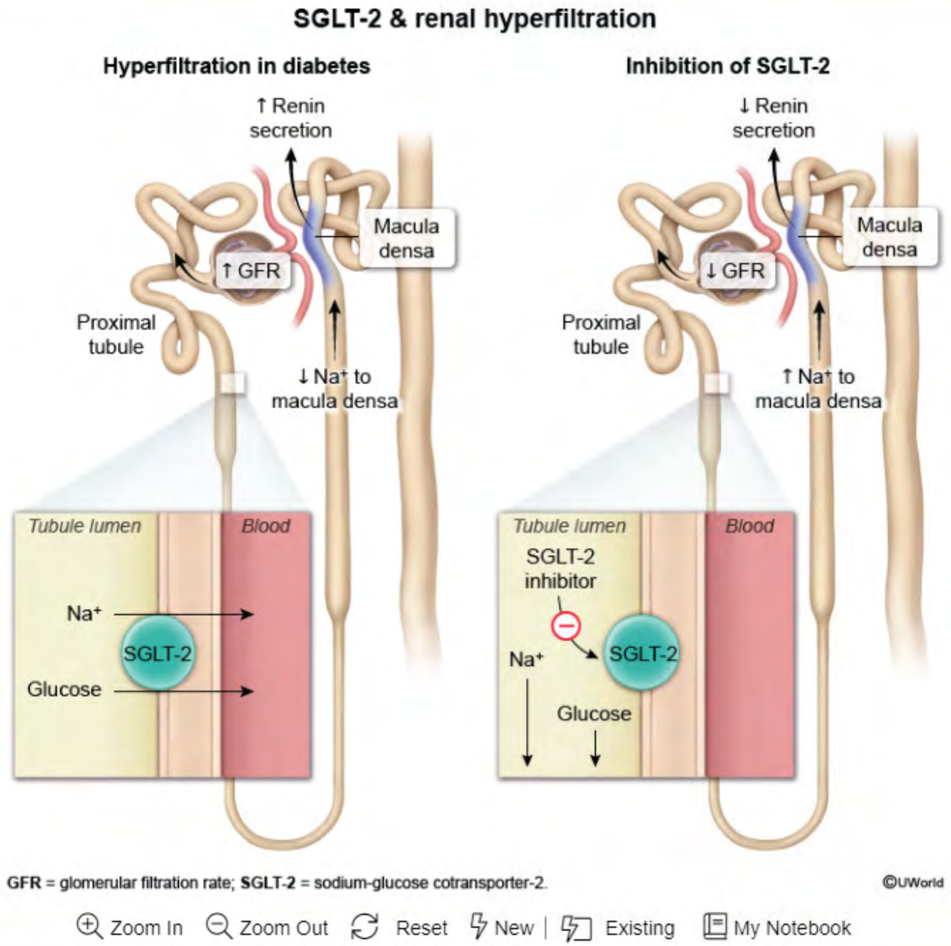
Explanation



https://t.me/USMLEWorldStep1

A 56-year-old man with type 2 diabetes mellitus, hypertension, and hyperlipidemia comes to the office due to
elevat
Blood
Labora
8.1%,
Which

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

This patient has incipient **diabetic nephropathy** with moderately increased albuminuria (ie, 30-300 mg/g). Although patients with more advanced diabetic kidney disease typically have reduced glomerular filtration (rising serum creatinine), in earlier stages, filtration is normal to increased and serum creatinine may be normal.

In the kidneys, glucose is freely filtered in the glomerulus and is normally reabsorbed with sodium by **sodium-glucose cotransporter-2** (SGLT2) in the proximal tubule. In patients with diabetes mellitus, the increased filtered glucose load leads to the following pathophysiologic changes:

- Reabsorption of the excess tubular glucose causes increased co-reabsorption of sodium by SGLT2.
- This results in **decreased tubular sodium delivery** to the macula densa, stimulating renin secretion by the juxtaglomerular apparatus and, ultimately, increasing angiotensin II levels.
- Angiotensin II induces relative vasoconstriction in the renal efferent arterioles, increasing hydrostatic pressure in the glomerular capillaries, contributing to **glomerular hyperfiltration**.

SGLT2 inhibitors (eg, empagliflozin) lower blood glucose levels by decreasing the reabsorption of glucose (and sodium) in the proximal tubule, causing urine glucose wasting and increased sodium excretion. The concurrent increase in tubular sodium delivery to the macula densa leads to decreased renin secretion, lower glomerular pressure, **reduced hyperfiltration**, and delayed progression of nephropathy.

(Choice A) Glucose is absorbed in the intestine primarily via SGLT1 (not SGLT2), which is not significantly affected by empagliflozin.

(Choices B and C) SGLT2 inhibitors lower blood glucose levels, leading to decreased secretion of insulin by pancreatic beta cells. Most patients taking SGLT2 inhibitors experience modest weight loss, not gain, due to urinary glucose wasting and lower circulating insulin levels.

(Choice E) SGLT2 inhibitors are associated with increased, not suppressed, glucagon secretion, possibly due to lower blood glucose and insulin levels or a direct effect on pancreatic alpha cells. Glucagon-like peptide-1 agonists (eg, exenatide) lower blood glucose levels by increasing glucose-dependent insulin secretion and suppressing glucagon secretion.

Educational objective:

https://t.me/USMLEWorldStep1

glucose load leads to the following pathophysiologic changes:

- Reabsorption of the excess tubular glucose causes increased co-reabsorption of sodium by SGLT2.
- This results in **decreased tubular sodium delivery** to the macula densa, stimulating renin secretion by the juxtaglomerular apparatus and, ultimately, increasing angiotensin II levels.
- Angiotensin II induces relative vasoconstriction in the renal efferent arterioles, increasing hydrostatic pressure in the glomerular capillaries, contributing to **glomerular hyperfiltration**.

SGLT2 inhibitors (eg, empagliflozin) lower blood glucose levels by decreasing the reabsorption of glucose (and sodium) in the proximal tubule, causing urine glucose wasting and increased sodium excretion. The concurrent increase in tubular sodium delivery to the macula densa leads to decreased renin secretion, lower glomerular pressure, **reduced hyperfiltration**, and delayed progression of nephropathy.

(Choice A) Glucose is absorbed in the intestine primarily via SGLT1 (not SGLT2), which is not significantly affected by empagliflozin.

(Choices B and C) SGLT2 inhibitors lower blood glucose levels, leading to decreased secretion of insulin by pancreatic beta cells. Most patients taking SGLT2 inhibitors experience modest weight loss, not gain, due to urinary glucose wasting and lower circulating insulin levels.

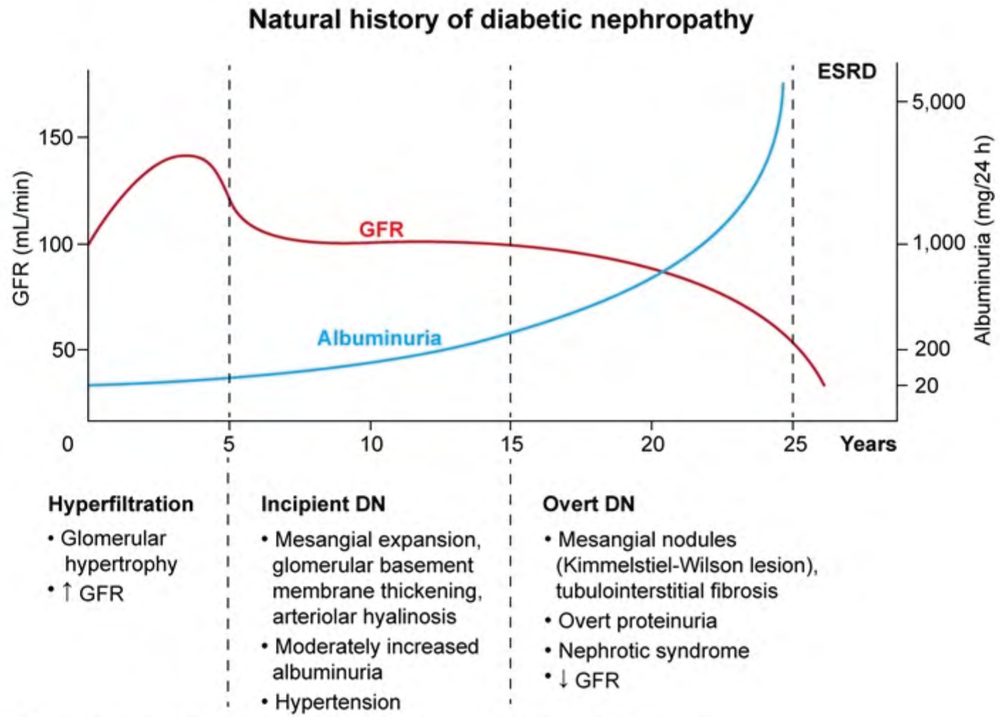
(Choice E) SGLT2 inhibitors are associated with increased, not suppressed, glucagon secretion, possibly due to lower blood glucose and insulin levels or a direct effect on pancreatic alpha cells. Glucagon-like peptide-1 agonists (eg, exenatide) lower blood glucose levels by increasing glucose-dependent insulin secretion and suppressing glucagon secretion.

Educational objective:
In patients with diabetes mellitus, excess glucose in the proximal tubule causes increased concurrent reabsorption of sodium by sodium-glucose cotransporter-2 (SGLT2). This leads to decreased sodium delivery to the macula densa and increased renin secretion, which increases glomerular filtration pressure and promotes glomerular hyperfiltration. SGLT2 inhibitors increase sodium delivery to the macula densa, decreasing renin production and reducing hyperfiltration.

https://t.me/USMLEWorldStep1



Exhibit Display



DN = diabetic nephropathy; **ESRD** = end-stage renal disease; **GFR** = glomerular filtration rate.
©UWorld

Zoom In Zoom Out Reset New | Existing My Notebook

This p
Althou
serum

In the
gluco
glucos

- R
- T
- A

SGLT
sodiu
increa
pressu

(Choi
affecte

(Choices B and C) SGLT2 inhibitors lower blood glucose levels, leading to decreased secretion of insulin by

https://t.me/USMLEWorldStep1

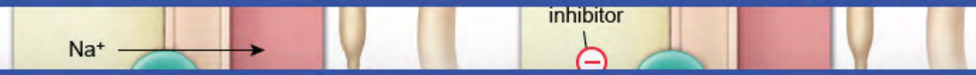
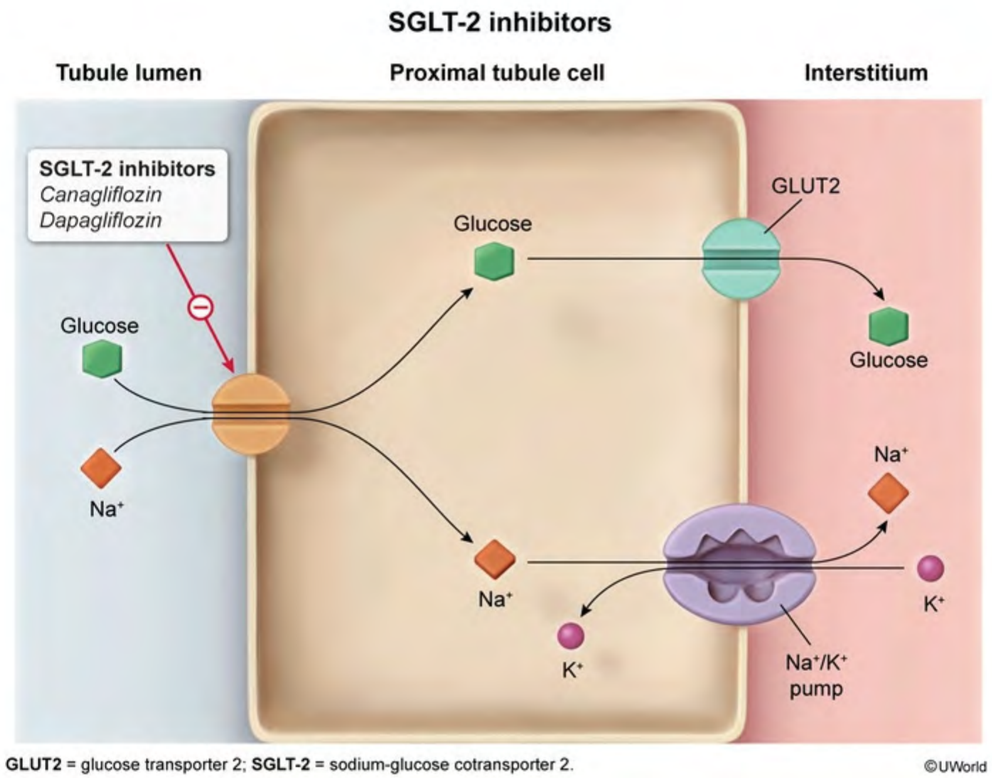


Exhibit Display



GLUT2 = glucose transporter 2; **SGLT-2** = sodium-glucose cotransporter 2.

©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

This p
Althou
serum

In the
gluco
glucos

- R
- T
  ju
- A
  in

SGLT
sodiu
increa
pressu

(Choi
affecte

(Choices B and C) SGLT2 inhibitors lower blood glucose levels, leading to decreased secretion of insulin by

https://t.me/USMLEWorldStep1

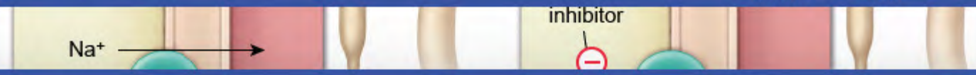
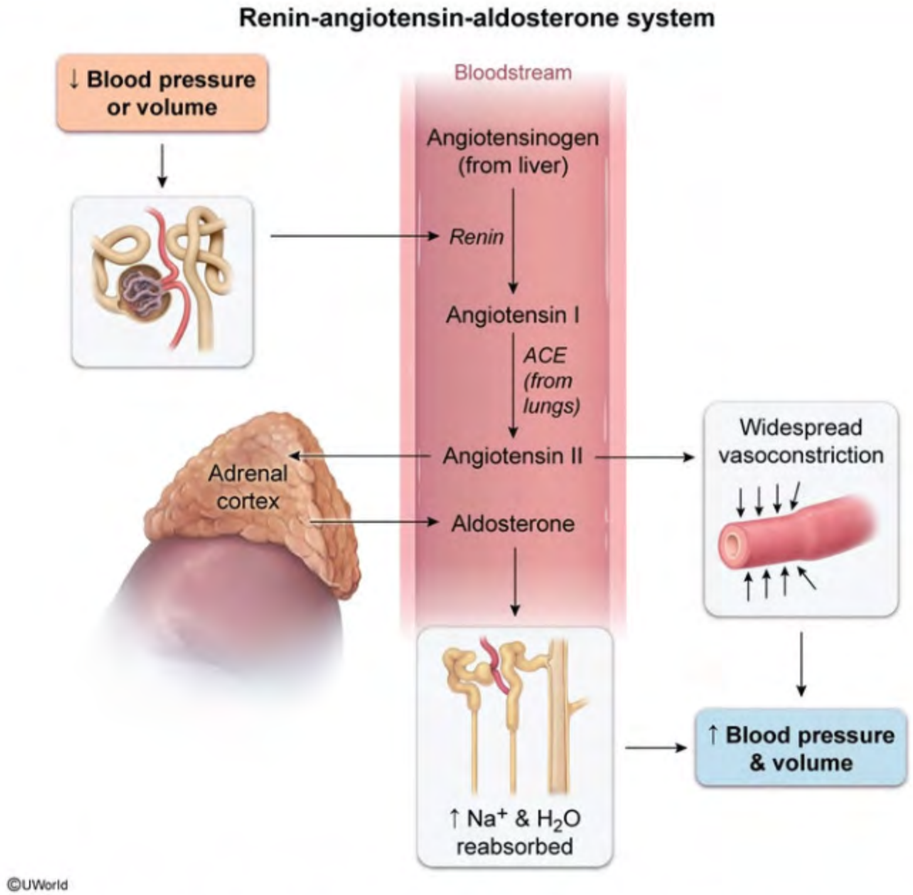


Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

This p
Althou
serum

In the
gluco
glucos

- R
- T
  ju
- A
  in

SGLT2
sodiu
increa
pressu

(Choi
affecte

(Choices B and C) SGLT2 inhibitors lower blood glucose levels, leading to decreased secretion of insulin by

https://t.me/USMLEWorldStep1

serum creatinine), in earlier stages, filtration is normal to increased and serum creatinine may be normal.

In the
gluco
glucos

- R
- T
  ju
- A
  in

SGLT2
sodiu
increa
pressu

(Choi
affecte

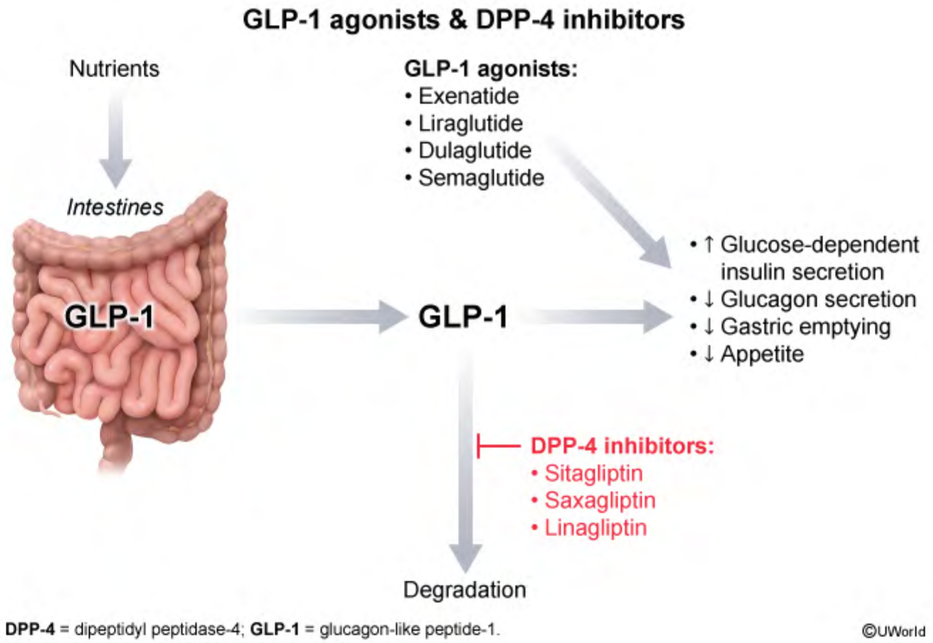
(Choi
pancre
urinary

(Choi
lower
(eg, ex
glucag

Educa
In pati

of sodium by sodium-glucose cotransporter-2 (SGLT2). This leads to decreased sodium delivery to the macula

Exhibit Display



Zoom In Zoom Out Reset New | Existing My Notebook

https://t.me/USMLEWorldStep1

A 35-year-old woman comes to the emergency department due to a "racing heart" and shortness of breath. She has had insomnia and increasing anxiety for the past several weeks. The patient has no prior medical problems and takes no medications. She has no drug allergies and does not use tobacco, alcohol, or illicit drugs. Blood pressure is 140/70 mm Hg and pulse is 120/min. Physical examination shows a diffusely enlarged, warm thyroid gland. There is a fine tremor in her outstretched hands. ECG shows sinus tachycardia. Serum TSH is decreased and free thyroxine (T4) is increased. The patient is treated with multiple drugs, including propranolol. In addition to its beta-adrenergic receptor-blocking activity, this drug is likely to decrease which of the following?

- A. Binding of triiodothyronine (T3) to its receptors
- B. New thyroid hormone synthesis
- C. Peripheral conversion of T4 to T3
- D. Release of T4 by the thyroid gland
- E. Serum levels of TSH receptor antibodies

Submit

https://t.me/USMLEWorldStep1

A 35-year-old woman comes to the emergency department due to a "racing heart" and shortness of breath. She has had insomnia and increasing anxiety for the past several weeks. The patient has no prior medical problems and takes no medications. She has no drug allergies and does not use tobacco, alcohol, or illicit drugs. Blood pressure is 140/70 mm Hg and pulse is 120/min. Physical examination shows a diffusely enlarged, warm thyroid gland. There is a fine tremor in her outstretched hands. ECG shows sinus tachycardia. Serum TSH is decreased and free thyroxine (T4) is increased. The patient is treated with multiple drugs, including propranolol. In addition to its beta-adrenergic receptor-blocking activity, this drug is likely to decrease which of the following?

- A. Binding of triiodothyronine (T3) to its receptors (11%)
- ✗ B. New thyroid hormone synthesis (7%)
- ✓ C. Peripheral conversion of T4 to T3 (69%)
- D. Release of T4 by the thyroid gland (9%)
- E. Serum levels of TSH receptor antibodies (1%)

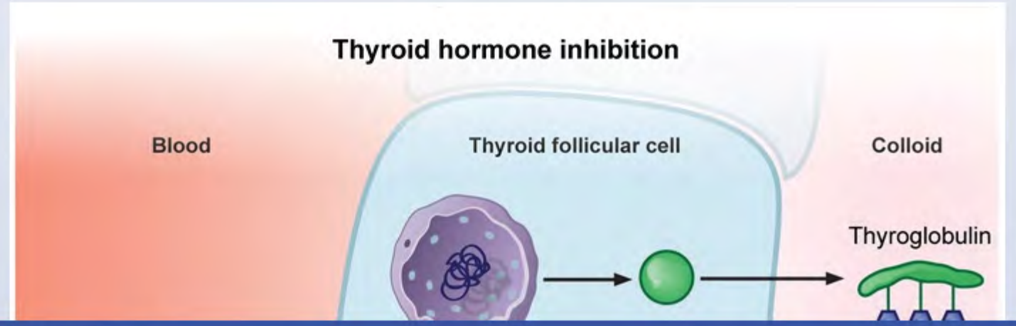
Incorrect
Correct answer
C

69%
Answered correctly

03 secs
Time Spent

2023
Version

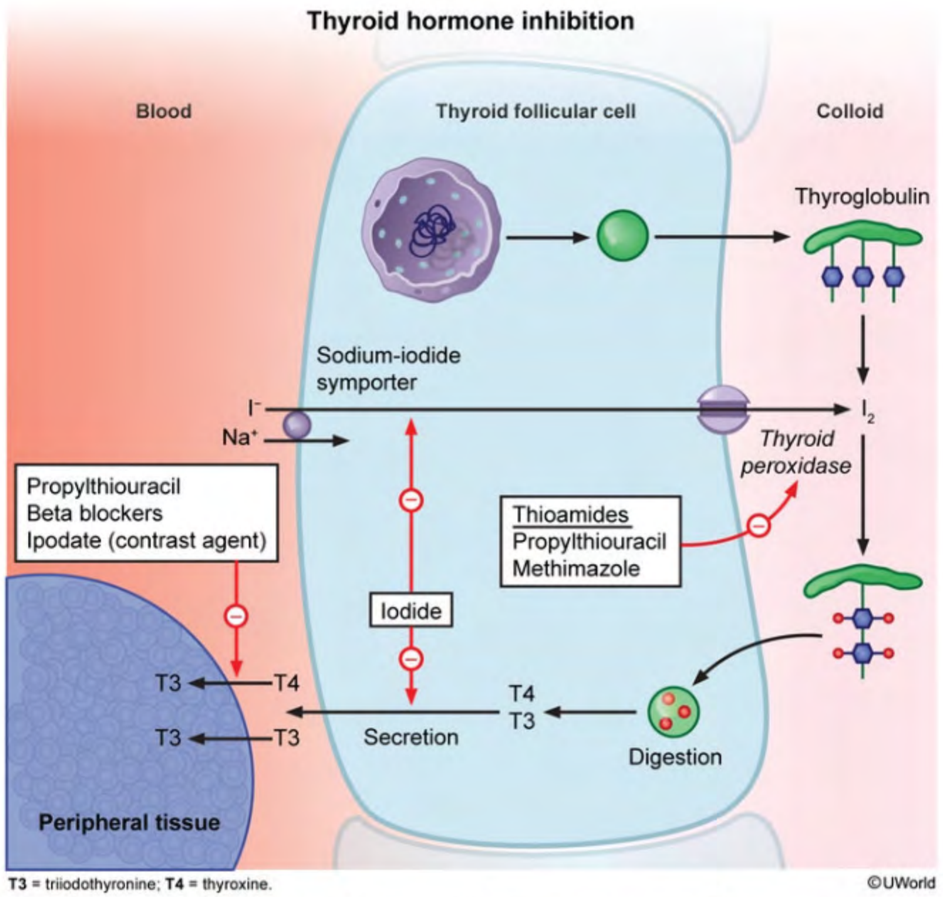
Explanation



https://t.me/USMLEWorldStep1

A 35-year-old woman comes to the emergency department due to a "racing heart" and shortness of breath. She has ha
and ta
pressu
gland.
and fre
its bet

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1



T3 = triiodothyronine; **T4** = thyroxine. ©UWorld

This patient has primary **hyperthyroidism** with an elevated thyroxine (T4) and suppressed TSH level. In light of her diffuse goiter, this is likely due to Graves disease. Hyperthyroidism causes **upregulation of beta-adrenergic receptor expression**, leading to **increased catecholamine effect** manifesting as hypertension, palpitations/tachycardia, heat intolerance, tremor, and hyperreflexia.

Beta blockers (eg, propranolol) are used to **blunt the adrenergic manifestations** of hyperthyroidism while awaiting definitive management (eg, surgery, radioiodine). In addition, lipid-soluble beta blockers (including propranolol) **reduce conversion of T4 to triiodothyronine (T3)**, the more active form of thyroid hormone, by inhibiting 5'-monodeiodinase in peripheral tissues. Peripheral conversion of T4 to T3 is also decreased by glucocorticoids and propylthiouracil.

(Choice A) The thyroid hormone receptor functions as a transcriptional modulator of several thyroid hormone–responsive genes. It is an intranuclear protein, and binding is not affected by beta blockers.

(Choices B and D) Thionamides (eg, propylthiouracil, methimazole) decrease thyroid hormone synthesis by inhibiting thyroid peroxidase. Iodine inhibits release of T4 and T3 from the thyroid. However, beta blockers do not alter thyroid hormone synthesis or release.

(Choice E) Graves disease is caused by autoantibodies that bind and stimulate the TSH receptor. Glucocorticoids and other immunosuppressive agents can decrease production of these antibodies, but beta blockers do not affect serum levels of TSH receptor antibodies.

Educational objective:
Hyperthyroidism causes upregulation of beta-adrenergic receptor expression, leading to increased catecholamine effect. Beta blockers are used to blunt the adrenergic manifestations of hyperthyroidism. In addition, lipid-soluble beta blockers reduce conversion of T4 to T3 by inhibiting 5'-monodeiodinase in peripheral tissues.

Pharmacology	Endocrine, Diabetes & Metabolism	Hyperthyroidism
Subject	System	Topic

Copyright © UWorld. All rights reserved.

https://t.me/USMLEWorldStep1

A 44-year-old man comes to the office for follow-up of type 2 diabetes mellitus. He was diagnosed 4 years ago and has since been taking metformin. Six months ago, a new antidiabetic agent was added because of suboptimal glycemic control. Today, the patient is pleased because he has unintentionally lost 7 kg (15.4 lb). His only symptoms are occasional nausea, vomiting, and a prolonged sensation of fullness after eating. Vital signs are within normal limits. BMI is 34 kg/m^2. Physical examination reveals normal heart and lung sounds, a nontender abdomen, and normal deep tendon reflexes. Laboratory testing shows normal renal function and a hemoglobin A1c of 7.2%. If this patient's weight loss is due to the new medication, which of the following agents is most likely responsible?

- A. Basal-bolus insulin therapy
- B. Dipeptidyl peptidase-4 inhibitor
- C. Glucagon-like peptide-1 agonist
- D. Sulfonylurea
- E. Thiazolidinedione

Submit

https://t.me/USMLEWorldStep1

A 44-year-old man comes to the office for follow-up of type 2 diabetes mellitus. He was diagnosed 4 years ago and has since been taking metformin. Six months ago, a new antidiabetic agent was added because of suboptimal glycemic control. Today, the patient is pleased because he has unintentionally lost 7 kg (15.4 lb). His only symptoms are occasional nausea, vomiting, and a prolonged sensation of fullness after eating. Vital signs are within normal limits. BMI is 34 kg/m^2. Physical examination reveals normal heart and lung sounds, a nontender abdomen, and normal deep tendon reflexes. Laboratory testing shows normal renal function and a hemoglobin A1c of 7.2%. If this patient's weight loss is due to the new medication, which of the following agents is most likely responsible?

- A. Basal-bolus insulin therapy (2%)
- ✗ B. Dipeptidyl peptidase-4 inhibitor (16%)
- ✓ C. Glucagon-like peptide-1 agonist (59%)
- D. Sulfonylurea (11%)
- E. Thiazolidinedione (10%)

Incorrect
Correct answer
C

59%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

Weight-favorable antidiabetic medications	
Weight-loss medications	• GLP-1 agonist ◦ Decreases gastric emptying ◦ Increases satiety (hypothalamic effect) • SGLT-2 inhibitor ◦ Increases glucosuria

https://t.me/USMLEWorldStep1

Weight-favorable antidiabetic medications	
Weight-loss medications	• GLP-1 agonist ◦ Decreases gastric emptying ◦ Increases satiety (hypothalamic effect) • SGLT-2 inhibitor ◦ Increases glucosuria
Weight-neutral medications	• DPP-4 inhibitor ◦ Inhibits metabolism of GLP-1 • Metformin ◦ Suppresses hepatic gluconeogenesis ◦ Decreases gastrointestinal glucose absorption
DPP-4 = dipeptidyl peptidase-4; **GLP-1** = glucagon-like peptide-1; **SGLT-2** = sodium-glucose cotransporter-2.	

This patient with inadequately controlled diabetes on metformin therapy was prescribed a second medication. The new agent is associated with nausea, vomiting, early satiety, and significant weight loss, effects characteristic of a **glucagon-like peptide-1 (GLP-1) agonist** (eg, exenatide, liraglutide).

GLP-1 is secreted by intestinal L cells in response to food intake and regulates glucose by **slowing gastric emptying**, suppressing glucagon secretion, and increasing **glucose-dependent insulin release** (ie, insulin release in response to food intake), which lowers the risk for hypoglycemia. It acts through cell surface receptors that are coupled with a G protein–adenylyl cyclase system. Native GLP-1 is degraded by dipeptidyl peptidase-4 (DPP-4), but synthetic GLP-1 agonists are more resistant to degradation, prolonging their therapeutic effect.

Although insulin secretion is increased by GLP-1 agonists, most patients **lose weight** due to **suppressed appetite** caused by the following:

- Slowed gastric emptying
- Nausea and vomiting

https://t.me/USMLEWorldStep1

This patient with inadequately controlled diabetes on metformin therapy was prescribed a second medication. The new agent is associated with nausea, vomiting, early satiety, and significant weight loss, effects characteristic of a **glucagon-like peptide-1 (GLP-1) agonist** (eg, exenatide, liraglutide).

GLP-1 is secreted by intestinal L cells in response to food intake and regulates glucose by **slowing gastric emptying**, suppressing glucagon secretion, and increasing **glucose-dependent insulin release** (ie, insulin release in response to food intake), which lowers the risk for hypoglycemia. It acts through cell surface receptors that are coupled with a G protein–adenylyl cyclase system. Native GLP-1 is degraded by dipeptidyl peptidase-4 (DPP-4), but synthetic GLP-1 agonists are more resistant to degradation, prolonging their therapeutic effect.

Although insulin secretion is increased by GLP-1 agonists, most patients **lose weight** due to **suppressed appetite** caused by the following:

- Slowed gastric emptying
- Nausea and vomiting
- **Increased satiety** (mediated by receptors in the hypothalamus)

These effects are also seen in patients without diabetes, a reason that certain GLP-1 agonists are also approved for the primary indication of weight loss.

(Choice A) Basal-bolus insulin therapy is typically used to treat patients with severe diabetes mellitus (eg, hemoglobin A1c >10%). Insulin therapy is not associated with gastrointestinal side effects but causes significant weight gain.

(Choice B) DPP-4 inhibitors (eg, sitagliptin) are oral agents that block the degradation of endogenous GLP-1. Because they act indirectly on the GLP-1 receptor, their effects (eg, antihyperglycemic, weight loss–related) are less pronounced compared to GLP-1 agonists, which act directly on the receptor. Therefore, these agents do not result in weight loss but are considered weight neutral.

(Choice D) Sulfonylureas directly stimulate pancreatic insulin secretion independent of circulating glucose levels, resulting in significant weight gain and risk for hypoglycemia.

(Choice E) Thiazolidinediones (eg, pioglitazone) increase the transcription of certain insulin-responsive genes and

https://t.me/USMLEWorldStep1

that are coupled with a G protein–adenylyl cyclase system. Native GLP-1 is degraded by dipeptidyl peptidase-4 (DPP-4), but synthetic GLP-1 agonists are more resistant to degradation, prolonging their therapeutic effect.

Although insulin secretion is increased by GLP-1 agonists, most patients **lose weight** due to **suppressed appetite** caused by the following:

- Slowed gastric emptying
- Nausea and vomiting
- **Increased satiety** (mediated by receptors in the hypothalamus)

These effects are also seen in patients without diabetes, a reason that certain GLP-1 agonists are also approved for the primary indication of weight loss.

(Choice A) Basal-bolus insulin therapy is typically used to treat patients with severe diabetes mellitus (eg, hemoglobin A1c >10%). Insulin therapy is not associated with gastrointestinal side effects but causes significant weight gain.

(Choice B) DPP-4 inhibitors (eg, sitagliptin) are oral agents that block the degradation of endogenous GLP-1. Because they act indirectly on the GLP-1 receptor, their effects (eg, antihyperglycemic, weight loss–related) are less pronounced compared to GLP-1 agonists, which act directly on the receptor. Therefore, these agents do not result in weight loss but are considered weight neutral.

(Choice D) Sulfonylureas directly stimulate pancreatic insulin secretion independent of circulating glucose levels, resulting in significant weight gain and risk for hypoglycemia.

(Choice E) Thiazolidinediones (eg, pioglitazone) increase the transcription of certain insulin-responsive genes and decrease insulin resistance. Weight gain and fluid retention are common side effects; weight loss is not seen.

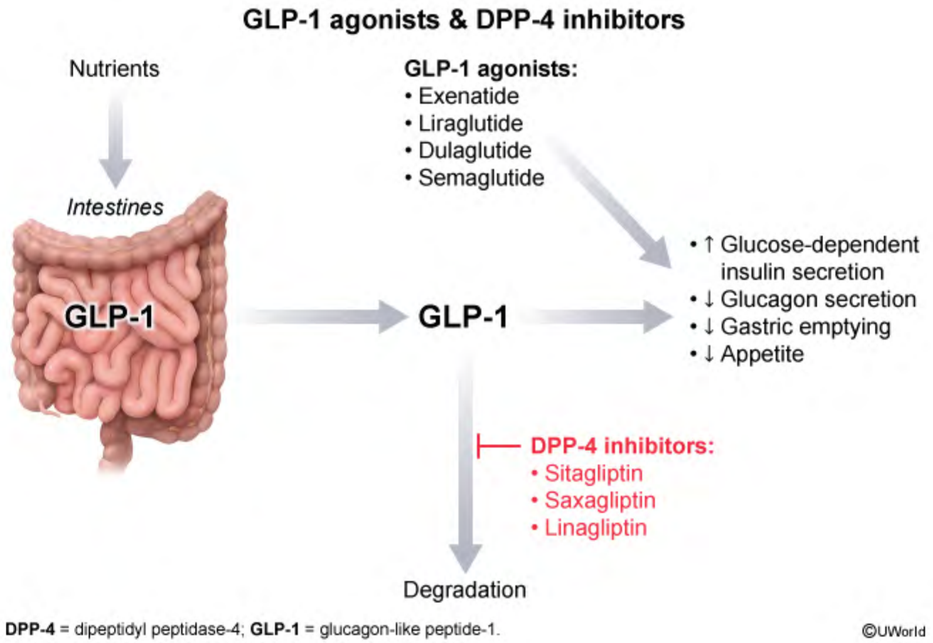
Educational objective:
Glucagon-like peptide-1 (GLP-1) agonists slow gastric emptying, suppress glucagon secretion, and increase glucose-dependent insulin release. These agents cause significant weight loss by suppressing the appetite and increasing satiety.

References

https://t.me/USMLEWorldStep1

- Decreases gastrointestinal glucose absorption

Exhibit Display



Zoom In Zoom Out Reset New | Existing My Notebook

This p
new a
gluca

GLP-1
empty
releas
that ar
(DPP-

Althou
cause

- S
- N
- **Ir**

These
for the

(Choi
hemog
weight

(Choi
Becau
less pr
result in weight loss but are considered weight neutral.

https://t.me/USMLEWorldStep1

A 48-year-old man comes to establish care after moving to a new state. He feels well and has no symptoms. The patient has a history of type 2 diabetes mellitus diagnosed 6 months ago; he was prescribed metformin by his previous physician but stopped taking it due to diarrhea. He was unable to follow up with the physician and has not taken any other medications. The patient exercises regularly and follows a low-carbohydrate diet. Laboratory results show a fasting blood glucose of 140 mg/dL and a hemoglobin A1c of 7.5%. The physician counsels the patient about adding canagliflozin to optimize glycemic control. Which of the following tests should be ordered prior to initiating this new medication?

- A. Leukocyte count
- B. Serum creatinine
- C. Serum uric acid
- D. Thyroid function tests
- E. Urinalysis

Submit

https://t.me/USMLEWorldStep1

A 48-year-old man comes to establish care after moving to a new state. He feels well and has no symptoms. The patient has a history of type 2 diabetes mellitus diagnosed 6 months ago; he was prescribed metformin by his previous physician but stopped taking it due to diarrhea. He was unable to follow up with the physician and has not taken any other medications. The patient exercises regularly and follows a low-carbohydrate diet. Laboratory results show a fasting blood glucose of 140 mg/dL and a hemoglobin A1c of 7.5%. The physician counsels the patient about adding canagliflozin to optimize glycemic control. Which of the following tests should be ordered prior to initiating this new medication?

- ✗ A. Leukocyte count (3%)
- ✓ B. Serum creatinine (60%)
- C. Serum uric acid (3%)
- D. Thyroid function tests (3%)
- E. Urinalysis (29%)

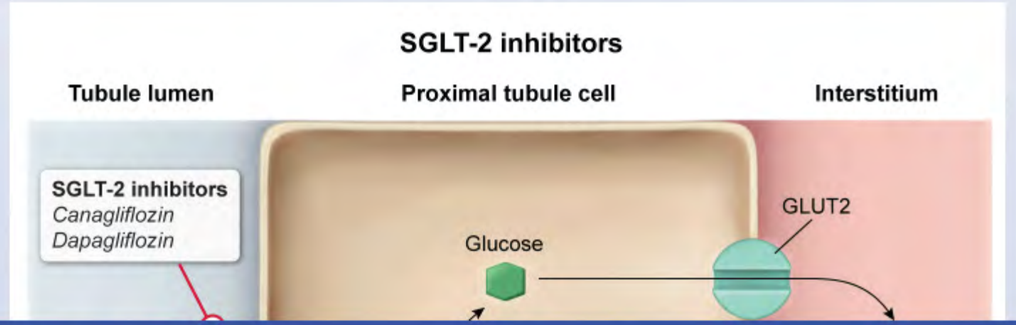
Incorrect
Correct answer
B

60%
Answered correctly

04 secs
Time Spent

2023
Version

Explanation

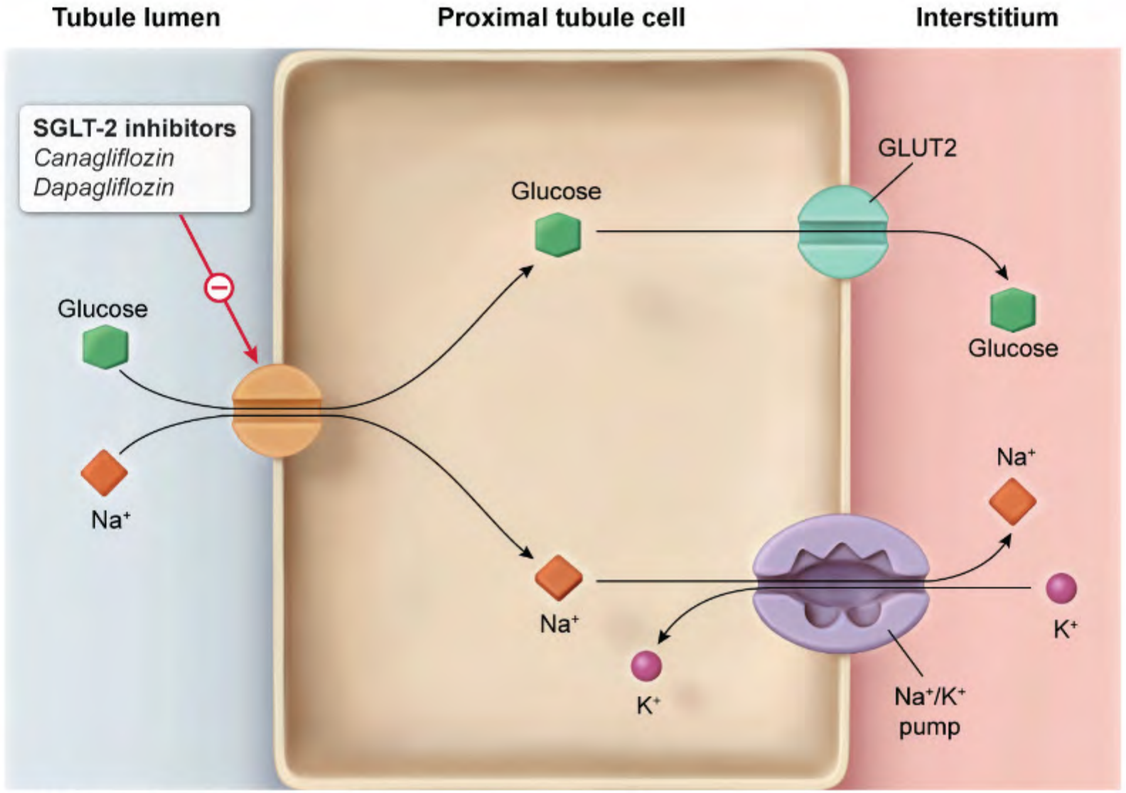


https://t.me/USMLEWorldStep1

B. Serum creatinine (60%)

Exhibit Display

SGLT-2 inhibitors



GLUT2 = glucose transporter 2; **SGLT-2** = sodium-glucose cotransporter 2.

©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1



GLUT2 = glucose transporter 2; **SGLT-2** = sodium-glucose cotransporter 2. ©UWorld

Sodium-glucose cotransporter-2 (SGLT-2) is a low-affinity, high-capacity transport protein that reabsorbs 90% of filtered glucose in the proximal tubule. **SGLT-2 inhibitors** (eg, canagliflozin, dapagliflozin) are oral antidiabetic agents that **decrease renal reabsorption** of sodium and **glucose** and thereby decrease blood glucose levels. They are used primarily as a combination therapy (eg, with metformin), especially in patients with atherosclerotic cardiovascular disease (eg, prior myocardial infarction), heart failure, or nephropathy (eg, albuminuria).

Because SGLT-2 inhibitors rely on adequate renal glucose filtration to exert their **antihyperglycemic effect**, they become **less effective** or ineffective as **renal function declines** (eg, when estimated glomerular filtration rate [eGFR] falls <30-45 mL/min/1.73 m^2). Therefore, checking serum **creatinine** (used to calculate eGFR) is recommended prior to medication initiation.

(Choices A and E) Although SGLT-2 inhibitors increase the risk for genitourinary infections (eg, candidiasis, urinary tract infection), screening for infection with a leukocyte count and urinalysis in asymptomatic patients (eg, no dysuria or fever) is unnecessary.

(Choice C) Certain drugs such as diuretics (eg, thiazide, loop) reduce renal uric acid clearance and may precipitate gout. However, SGLT-2 inhibitors are associated with increased renal uric acid clearance and are not expected to increase the risk for gout.

(Choice D) Thyroid function tests are routinely performed on patients taking lithium and amiodarone, which can alter thyroid hormone metabolism. However, thyroid function tests are not required for antidiabetic medications.

Educational objective:
Sodium-glucose cotransporter-2 inhibitors (eg, canagliflozin, dapagliflozin) lower glucose levels by decreasing renal reabsorption of glucose and have cardioprotective and renoprotective effects. Checking serum creatinine is recommended prior to initiation because the antihyperglycemic effect of these medications becomes less pronounced as renal function declines.

References

https://t.me/USMLEWorldStep1

A 37-year-old woman comes to the office due to a two-month history of abdominal pain, salt craving, and weight loss. She also has dizziness on standing. The patient has no chronic medical conditions and takes no medications. She does not use tobacco, alcohol, or illicit drugs. Her mother and sister have hypothyroidism. Blood pressure is 100/70 mm Hg supine and 80/50 mm Hg standing. Laboratory results are as follows:

Sodium	129 mEq/L
Potassium	5.9 mEq/L
Chloride	100 mEq/L
Bicarbonate	21 mEq/L
Creatinine	1.4 mg/dL
Blood urea nitrogen	38 mg/dL

Which of the following changes in circulating hormone levels are expected in this patient?

	Cortisol	Aldosterone	Antidiuretic hormone	Norepinephrine
A.	↓	↓	↑	↑
B.	Normal	Normal	↑	Normal
C.	Normal	↑	↑	↑
D.	↓	↑	↑	↑
E.	↑	↑	↑	↑
F.	↑	↓	↓	↓

Submit

https://t.me/USMLEWorldStep1

A 37-year-old woman comes to the office due to a two-month history of abdominal pain, salt craving, and weight loss. She also has dizziness on standing. The patient has no chronic medical conditions and takes no medications. She does not use tobacco, alcohol, or illicit drugs. Her mother and sister have hypothyroidism. Blood pressure is 100/70 mm Hg supine and 80/50 mm Hg standing. Laboratory results are as follows:

Sodium	129 mEq/L
Potassium	5.9 mEq/L
Chloride	100 mEq/L
Bicarbonate	21 mEq/L
Creatinine	1.4 mg/dL
Blood urea nitrogen	38 mg/dL

Which of the following changes in circulating hormone levels are expected in this patient?

		Cortisol hormone	Aldosterone	Antidiuretic	Norepinephrine	
✓	A.	↓	↓	↑	↑	(66%)
	B.	Normal	Normal	↑	Normal	(2%)
	C.	Normal	↑	↑	↑	(5%)
	D.	↓	↑	↑	↑	(6%)
	E.	↑	↑	↑	↑	(7%)
	F.	↑	↓	↓	↓	(12%)

Correct

66% Answered correctly

04 secs Time Spent

2023 Version

https://t.me/USMLEWorldStep1

Explanation

This patient has multiple signs and symptoms of **primary adrenal insufficiency** (PAI) (also known as Addison disease), including abdominal pain, weight loss, salt craving, orthostasis (dizziness on standing), and electrolyte disturbance. PAI usually results from autoimmune destruction of the bilateral adrenal cortex and is more likely to occur in patients with a personal or family **history of autoimmune disease** (eg, Hashimoto thyroiditis). Because all 3 layers of the adrenal cortex are affected, clinical manifestations result from a reduction in circulating mineralocorticoids, glucocorticoids, and androgens.

Reduced aldosterone, the principal mineralocorticoid in the body, leads to markedly decreased sodium absorption by the renal collecting tubule principal cells with consequent retention of potassium (leading to **hyperkalemia**). The decrease in total body sodium results in **hypovolemia** and **hypotension** that may lead to renal insufficiency. The hypovolemia provides nonosmotic stimulus for **antidiuretic hormone (ADH) secretion**, which stimulates water retention and leads to **hyponatremia**.

Cortisol, the main glucocorticoid in the body, normally inhibits ADH secretion; therefore, **reduced cortisol** further contributes to hyponatremia. Cortisol is also necessary for the synthesis of epinephrine in the adrenal medulla; the consequent reduction in circulating epinephrine leads to a compensatory **increase in norepinephrine** to increase vascular tone in an effort to maintain blood pressure.

(Choice B) Increased ADH and normal levels of cortisol, aldosterone, and norepinephrine occur in the syndrome of inappropriate ADH secretion (SIADH). SIADH presents with hyponatremia, but it does not explain this patient's hyperkalemia, salt craving, and orthostatic symptoms.

(Choices C, D, and E) Elevations in aldosterone, ADH, and norepinephrine occur in conditions that decrease effective arterial blood volume and renal perfusion (eg, heart failure, cirrhosis, dehydration). Cortisol levels are often elevated in dehydration and heart failure; total cortisol is low in cirrhosis due to reduced cortisol-binding protein levels.

(Choice F) Increased cortisol with reduced levels of aldosterone, ADH, and norepinephrine can occur with ectopic ACTH production (eg, due to small cell lung cancer). Aldosterone synthesis is mostly independent of ACTH and is suppressed because cortisol and other glucocorticoids have some mineralocorticoid activity. Levels of ADH and norepinephrine are also generally suppressed.

https://t.me/USMLEWorldStep1

mineralocorticoids, glucocorticoids, and androgens.

Reduced aldosterone, the principal mineralocorticoid in the body, leads to markedly decreased sodium absorption by the renal collecting tubule principal cells with consequent retention of potassium (leading to **hyperkalemia**). The decrease in total body sodium results in **hypovolemia** and **hypotension** that may lead to renal insufficiency. The hypovolemia provides nonosmotic stimulus for **antidiuretic hormone (ADH) secretion**, which stimulates water retention and leads to **hyponatremia**.

Cortisol, the main glucocorticoid in the body, normally inhibits ADH secretion; therefore, **reduced cortisol** further contributes to hyponatremia. Cortisol is also necessary for the synthesis of epinephrine in the adrenal medulla; the consequent reduction in circulating epinephrine leads to a compensatory **increase in norepinephrine** to increase vascular tone in an effort to maintain blood pressure.

(Choice B) Increased ADH and normal levels of cortisol, aldosterone, and norepinephrine occur in the syndrome of inappropriate ADH secretion (SIADH). SIADH presents with hyponatremia, but it does not explain this patient's hyperkalemia, salt craving, and orthostatic symptoms.

(Choices C, D, and E) Elevations in aldosterone, ADH, and norepinephrine occur in conditions that decrease effective arterial blood volume and renal perfusion (eg, heart failure, cirrhosis, dehydration). Cortisol levels are often elevated in dehydration and heart failure; total cortisol is low in cirrhosis due to reduced cortisol-binding protein levels.

(Choice F) Increased cortisol with reduced levels of aldosterone, ADH, and norepinephrine can occur with ectopic ACTH production (eg, due to small cell lung cancer). Aldosterone synthesis is mostly independent of ACTH and is suppressed because cortisol and other glucocorticoids have some mineralocorticoid activity. Levels of ADH and norepinephrine are also generally suppressed.

Educational objective:
Primary adrenal insufficiency usually involves autoimmune destruction of the bilateral adrenal cortex. Reduced aldosterone production leads to renal salt wasting with hypovolemia, hypotension, and hyperkalemia. The hypovolemia and reduced cortisol-induced inhibition of antidiuretic hormone lead to water retention and hyponatremia. Reduced cortisol also causes decreased circulating epinephrine with a compensatory increase in norepinephrine.

https://t.me/USMLEWorldStep1

Correct
66% Answered correctly
04 secs Time Spent
2023 Version

Exhibit Display

Expl

This p
diseas
disturb
occur
all 3 la
minera

Reduc
by the
The de
The hy
water

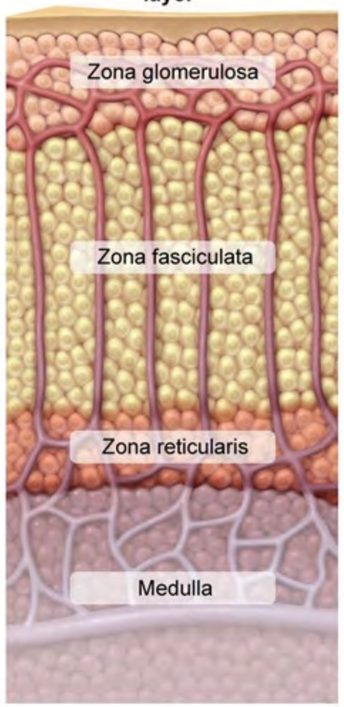
Cortis
contrib
conse
vascul

(Choi
of inap
hyperk

(Choi
effecti
often e
protein levels.

Adrenal cortical structure & function

Principal stimulatory hormone	Adrenal layer	Principal secreted hormone	Physiologic effect
Angiotensin II	Zona glomerulosa	Aldosterone	↑ Blood volume
ACTH	Zona fasciculata	Cortisol	↑ Vascular tone ↑ Blood glucose
ACTH	Zona reticularis	Androgens	Libido & pubic hair in women
	Medulla		



©UWorld

Zoom In Zoom Out Reset New | Existing My Notebook

https://t.me/USMLEWorldStep1

Correct

66%
Answered correctly

04 secs
Time Spent

2023
Version

Exhibit Display

Expl

This p
diseas
disturb
occur
all 3 la
minera

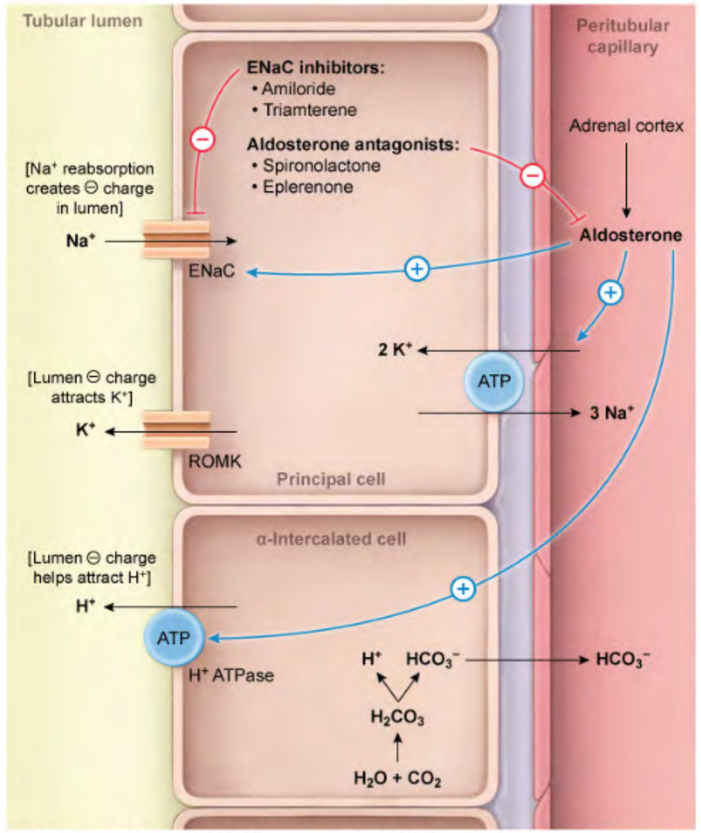
Reduc
by the
The de
The hy
water

Cortis
contrib
conse
vascul

(Choi
of inap
hyperk

(Choi
effecti
often e
protein levels.

Action of aldosterone in the collecting duct of the nephron



ENaC = epithelial sodium channel; **ROMK** = renal outer medullary potassium channel. ©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

A 32-year-old previously healthy woman comes to the office due to several weeks of anxiety, palpitations, excessive sweating, and thinning hair. The symptoms have progressively worsened and interfered significantly with her daily activities. The patient does not use tobacco, alcohol, or illicit drugs. Blood pressure is 130/70 mm Hg and pulse is 104/min. On physical examination, there is lid lag, moderate exophthalmos, and fine tremors of the outstretched hands. After the diagnosis is made, she is prescribed propranolol for immediate symptom control. Which of the following findings is most likely to persist in this patient despite this therapy?

- A. Anxiety
- B. Diaphoresis
- C. Exophthalmos
- D. Hand tremor
- E. Heat intolerance
- F. Palpitations

Submit

https://t.me/USMLEWorldStep1

A 32-year-old previously healthy woman comes to the office due to several weeks of anxiety, palpitations, excessive sweating, and thinning hair. The symptoms have progressively worsened and interfered significantly with her daily activities. The patient does not use tobacco, alcohol, or illicit drugs. Blood pressure is 130/70 mm Hg and pulse is 104/min. On physical examination, there is lid lag, moderate exophthalmos, and fine tremors of the outstretched hands. After the diagnosis is made, she is prescribed propranolol for immediate symptom control. Which of the following findings is most likely to persist in this patient despite this therapy?

- A. Anxiety (3%)
- ✗ B. Diaphoresis (6%)
- ✓ C. Exophthalmos (84%)
- D. Hand tremor (2%)
- E. Heat intolerance (2%)
- F. Palpitations (0%)

Incorrect
Correct answer
C

84%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

General manifestations of hyperthyroidism	
Symptoms	• Anxiety & insomnia • Palpitations • Heat intolerance • Increased perspiration • Weight loss without decreased

https://t.me/USMLEWorldStep1

General manifestations of hyperthyroidism	
Symptoms	• Anxiety & insomnia • Palpitations • Heat intolerance • Increased perspiration • Weight loss without decreased appetite
Physical examination	• Goiter • Hypertension • Tremors involving fingers/hands • Hyperreflexia • Proximal muscle weakness • Lid lag • Atrial fibrillation

Graves disease is an autoimmune disorder characterized by autoantibodies that bind to and activate the TSH receptor (**thyrotropin receptor antibodies** [TRAb]). In the thyroid, TRAb triggers release of thyroid hormones, leading to thyrotoxicosis. Hyperthyroidism causes increased expression of **beta-adrenergic receptors** in various organs, and the subsequent hyperadrenergic state can result in hypertension, tremor, heat intolerance, palpitations/tachycardia, and hyperreflexia **(Choices D, E, and F)**. Patients with Graves disease are frequently given beta-adrenergic blocking medications (eg, propranolol) to control these manifestations while awaiting definitive management.

TSH receptors are also present on fibroblasts, adipocytes, and other tissues. Graves ophthalmopathy results from stimulation of orbital fibroblasts and adipocytes by TRAb and activated T cells. The fibroblasts secrete excess amounts of glycosaminoglycans, leading to expansion of the ground substance of retro-orbital tissues. This, along with excess adipose deposition, displaces the globe forward (**exophthalmos**) and leads to restricted movement of

https://t.me/USMLEWorldStep1

Graves disease is an autoimmune disorder characterized by autoantibodies that bind to and activate the TSH receptor (**thyrotropin receptor antibodies** [TRAb]). In the thyroid, TRAb triggers release of thyroid hormones, leading to thyrotoxicosis. Hyperthyroidism causes increased expression of **beta-adrenergic receptors** in various organs, and the subsequent hyperadrenergic state can result in hypertension, tremor, heat intolerance, palpitations/tachycardia, and hyperreflexia **(Choices D, E, and F)**. Patients with Graves disease are frequently given beta-adrenergic blocking medications (eg, propranolol) to control these manifestations while awaiting definitive management.

TSH receptors are also present on fibroblasts, adipocytes, and other tissues. Graves ophthalmopathy results from stimulation of orbital fibroblasts and adipocytes by TRAb and activated T cells. The fibroblasts secrete excess amounts of glycosaminoglycans, leading to expansion of the ground substance of retro-orbital tissues. This, along with excess adipose deposition, displaces the globe forward (**exophthalmos**) and leads to restricted movement of the extraocular muscles (eg, diplopia). These manifestations are not mediated by thyroid hormone or adrenergic stimulation and do not respond to beta blockers. However, as they are **immune mediated**, the manifestations of Graves ophthalmopathy usually respond to **glucocorticoid therapy**.

(Choice A) Although beta blockers can cause fatigue and depressive symptoms, they help reduce fatigue and mood lability in patients with Graves disease by ameliorating sympathetic overactivation. Beta blockers can also help blunt the physical manifestations of anxiety.

(Choice B) Apocrine sweat glands are stimulated primarily by catecholamines; beta blockers can reduce secretory activity. By contrast, eccrine sweat glands are directly innervated by cholinergic fibers. However, centrally acting beta blockers (eg, propranolol) can modulate eccrine activity and reduce emotionally driven (eg, anxiety) stimulation of eccrine sweating.

Educational objective:
Hyperthyroidism causes a hyperadrenergic state characterized by hypertension, palpitations/tachycardia, sweating, heat intolerance, tremor, and hyperreflexia. Beta blockers can relieve these symptoms. Exophthalmos in Graves disease is due to an immune-mediated increase in orbital soft tissue mass and does not improve with beta blockers.

References

https://t.me/USMLEWorldStep1

Graves disease is an autoimmune disorder characterized by autoantibodies that bind to and activate the TSH recept
leadin
organs
palpita
given
definiti

TSH re
stimula
amoun
with e
the ex
stimula
Grave

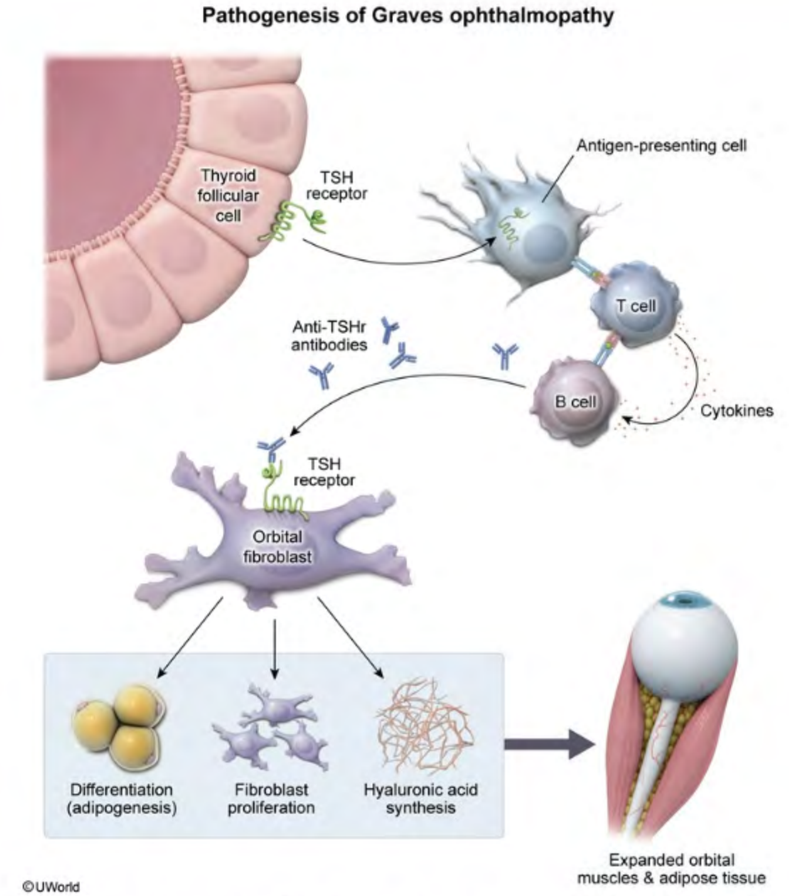
(Choi
mood
help b

(Choi
activity
beta b
stimula

Educa
Hyper
heat ir
diseas
blockers.

Reference

Exhibit Display



Zoom In Zoom Out Reset New | Existing My Notebook

https://t.me/USMLEWorldStep1

A 26-year-old woman comes to the clinic due to worsening generalized weakness, myalgias, and unintentional weight loss. She has primary hypothyroidism for which she takes levothyroxine. Blood pressure is 110/70 mm Hg supine and 90/60 mm Hg standing. She appears mildly emaciated. Cardiopulmonary examination reveals no abnormalities. Laboratory studies show mild normochromic, normocytic anemia; eosinophil count of 15%; and serum glucose of 65 mg/dL. Which of the following additional changes is most likely in this patient?

	Serum Na	Serum K	Urine Na	Urine K
○ A.	↓	↑	↑	↓
○ B.	↓	Normal	↑	Normal
○ C.	↓	↓	↓	↑
○ D.	↓	↑	↓	↑
○ E.	Normal	↓	Normal	↑

Submit

https://t.me/USMLEWorldStep1

A 26-year-old woman comes to the clinic due to worsening generalized weakness, myalgias, and unintentional weight loss. She has primary hypothyroidism for which she takes levothyroxine. Blood pressure is 110/70 mm Hg supine and 90/60 mm Hg standing. She appears mildly emaciated. Cardiopulmonary examination reveals no abnormalities. Laboratory studies show mild normochromic, normocytic anemia; eosinophil count of 15%; and serum glucose of 65 mg/dL. Which of the following additional changes is most likely in this patient?

	Serum Na	Serum K	Urine Na	Urine K	
✓ A.	↓	↑	↑	↓	(55%)
B.	↓	Normal	↑	Normal	(11%)
C.	↓	↓	↓	↑	(13%)
D.	↓	↑	↓	↑	(9%)
E.	Normal	↓	Normal	↑	(10%)

Correct

55% Answered correctly

03 secs Time Spent

2023 Version

Explanation

This patient has multiple clinical features that suggest **primary adrenal insufficiency** (PAI) (also known as Addison disease). PAI most commonly results from autoimmune destruction of the bilateral adrenal cortex and often occurs in patients with a preexisting history of **autoimmune disease** (eg, hypothyroidism, type 1 diabetes mellitus). Reduced mineralocorticoid (mainly aldosterone) production leads to renal salt wasting with consequent **hypovolemia and orthostasis** (systolic blood pressure decrease ≥20 mm Hg with standing). Reduced cortisol can lead to **hypoglycemia**, normocytic **anemia**, and **eosinophilia**.

In the renal collecting tubule principal cells, reduced aldosterone leads to markedly decreased sodium absorption

https://t.me/USMLEWorldStep1

This patient has multiple clinical features that suggest **primary adrenal insufficiency** (PAI) (also known as Addison disease). PAI most commonly results from autoimmune destruction of the bilateral adrenal cortex and often occurs in patients with a preexisting history of **autoimmune disease** (eg, hypothyroidism, type 1 diabetes mellitus). Reduced mineralocorticoid (mainly aldosterone) production leads to renal salt wasting with consequent **hypovolemia and orthostasis** (systolic blood pressure decrease ≥20 mm Hg with standing). Reduced cortisol can lead to **hypoglycemia**, normocytic **anemia**, and **eosinophilia**.

In the renal collecting tubule principal cells, reduced aldosterone leads to markedly decreased sodium absorption and increased potassium absorption; therefore, there is **high urine sodium** and **low urine potassium**. Serum potassium is elevated **(hyperkalemia)** due to the increased tubular absorption. Although the tubular salt wasting reduces total body sodium, it does not directly affect serum sodium concentration. However, because hypovolemia provides nonosmotic stimulus for antidiuretic hormone (ADH) secretion and ADH secretion is normally inhibited by cortisol, ADH levels are increased in PAI. The increased ADH levels lead to increased water retention and low serum sodium **(hyponatremia)**.

(Choice B) Hyponatremia in the setting of high urine sodium is characteristic of the syndrome of inappropriate ADH secretion (SIADH). SIADH has no significant effect on serum and urine potassium levels.

(Choices C and D) In hypovolemic states (eg, severe vomiting, diabetic ketoacidosis), restoration of blood volume is the highest priority. Therefore, the kidneys respond by stimulating increased aldosterone secretion, which decreases urine sodium and increases urine potassium. The hypovolemia also provides nonosmotic stimulus for ADH release, which leads to hyponatremia. Both total body and serum potassium are low in severe vomiting due to both gastrointestinal and renal losses. Although total body potassium is low in diabetic ketoacidosis, serum potassium is high because potassium is unable to enter cells in the absence of insulin.

(Choice E) Primary hyperaldosteronism causes potassium wasting by the renal principal cells, leading to high urine potassium and low serum potassium (hypokalemia). There is renal sodium retention that leads to increased blood volume, but any significant change in serum or urine sodium concentration is avoided due to aldosterone escape.

Educational objective:

https://t.me/USMLEWorldStep1

often occurs in patients with a preexisting history of **autoimmune disease** (eg, hypothyroidism, type 1 diabetes mellitus). Reduced mineralocorticoid (mainly aldosterone) production leads to renal salt wasting with consequent **hypovolemia and orthostasis** (systolic blood pressure decrease ≥20 mm Hg with standing). Reduced cortisol can lead to **hypoglycemia**, normocytic **anemia**, and **eosinophilia**.

In the renal collecting tubule principal cells, reduced aldosterone leads to markedly decreased sodium absorption and increased potassium absorption; therefore, there is **high urine sodium** and **low urine potassium**. Serum potassium is elevated **(hyperkalemia)** due to the increased tubular absorption. Although the tubular salt wasting reduces total body sodium, it does not directly affect serum sodium concentration. However, because hypovolemia provides nonosmotic stimulus for antidiuretic hormone (ADH) secretion and ADH secretion is normally inhibited by cortisol, ADH levels are increased in PAI. The increased ADH levels lead to increased water retention and low serum sodium **(hyponatremia)**.

(Choice B) Hyponatremia in the setting of high urine sodium is characteristic of the syndrome of inappropriate ADH secretion (SIADH). SIADH has no significant effect on serum and urine potassium levels.

(Choices C and D) In hypovolemic states (eg, severe vomiting, diabetic ketoacidosis), restoration of blood volume is the highest priority. Therefore, the kidneys respond by stimulating increased aldosterone secretion, which decreases urine sodium and increases urine potassium. The hypovolemia also provides nonosmotic stimulus for ADH release, which leads to hyponatremia. Both total body and serum potassium are low in severe vomiting due to both gastrointestinal and renal losses. Although total body potassium is low in diabetic ketoacidosis, serum potassium is high because potassium is unable to enter cells in the absence of insulin.

(Choice E) Primary hyperaldosteronism causes potassium wasting by the renal principal cells, leading to high urine potassium and low serum potassium (hypokalemia). There is renal sodium retention that leads to increased blood volume, but any significant change in serum or urine sodium concentration is avoided due to aldosterone escape.

Educational objective:
Reduced aldosterone production in primary adrenal insufficiency leads to renal sodium wasting with consequent hypovolemia, orthostasis, and potassium retention (hyperkalemia). Low cortisol stimulates increased antidiuretic hormone secretion, which leads to water retention and hyponatremia.

https://t.me/USMLEWorldStep1

Answered correctly
Time Spent
Version

Exhibit Display

Adrenal cortical structure & function

Principal stimulatory hormone	Adrenal layer	Principal secreted hormone	Physiologic effect
Angiotensin II	Zona glomerulosa	Aldosterone	↑ Blood volume
ACTH	Zona fasciculata	Cortisol	↑ Vascular tone ↑ Blood glucose
ACTH	Zona reticularis	Androgens	Libido & pubic hair in women
	Medulla		

©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

This p
Addis
often
mellitu
hypov
can le

In the
and in
potass
reduce
provid
cortisc
serum

(Choi
ADH s

(Choi
is the
decrea
ADH r
to both
potass

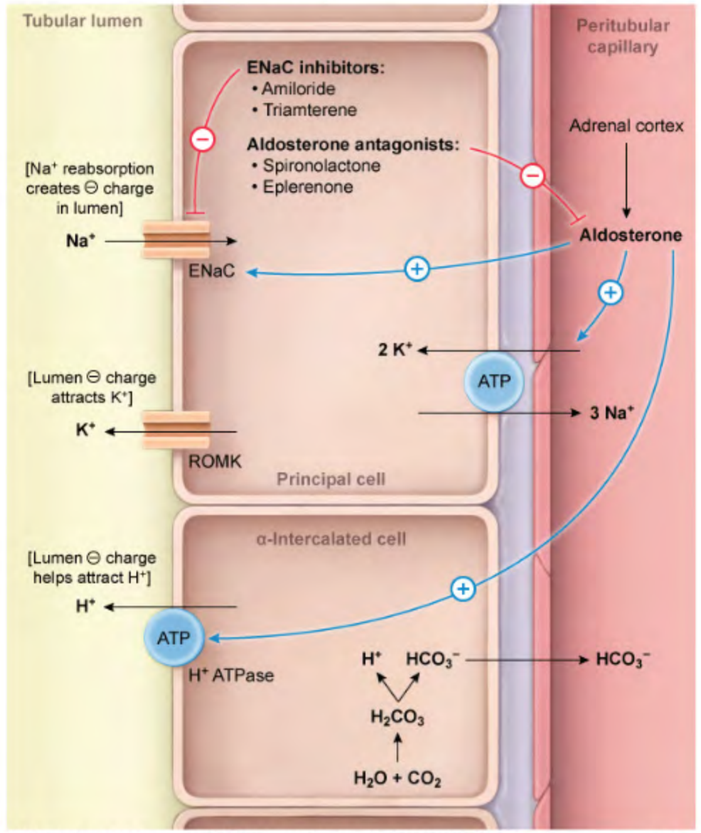
(Choice E) Primary hyperaldosteronism causes potassium wasting by the renal principal cells, leading to high urine potassium and low serum potassium (hypokalemia). There is renal sodium retention that leads to increased

https://t.me/USMLEWorldStep1

Answered correctly
Time Spent
Version

Exhibit Display

Action of aldosterone in the collecting duct of the nephron



ENaC = epithelial sodium channel; **ROMK** = renal outer medullary potassium channel. ©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

This p
Addis
often
mellitu
hypov
can le

In the
and in
potass
reduce
provid
cortisc
serum

(Choi
ADH s

(Choi
is the
decrea
ADH r
to both
potass

(Choice E) Primary hyperaldosteronism causes potassium wasting by the renal principal cells, leading to high urine potassium and low serum potassium (hypokalemia). There is renal sodium retention that leads to increased

https://t.me/USMLEWorldStep1

often occurs in patients with a preexisting history of **autoimmune disease** (eg, hypothyroidism, type 1 diabetes mellitus). Reduced mineralocorticoid (mainly aldosterone) production leads to renal salt wasting with consequent **hypov**
can le

In the
and in
potass
reduce
provid
cortisc
serum

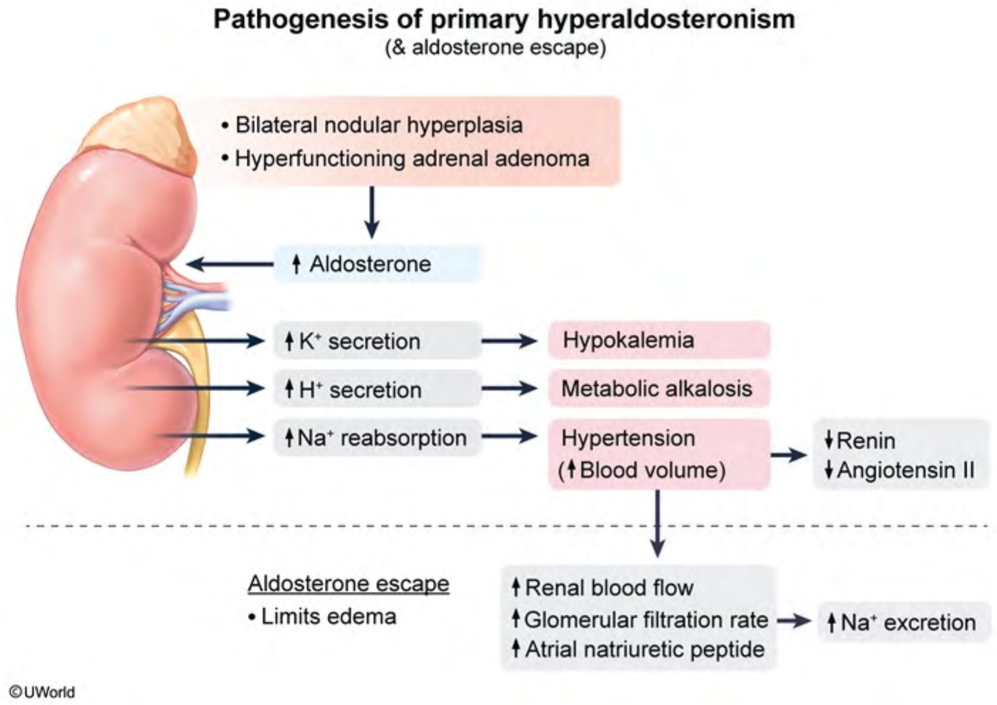
(Choi
ADH s

(Choi
is the
decrea
ADH r
to both
potass

(Choi
urine p
blood
escape

Educa
Reduc
hypov

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

hormone secretion, which leads to water retention and hyponatremia.

https://t.me/USMLEWorldStep1

A 46-year-old woman comes to the office due to frequent episodes of headache, nausea, sweating, and a feeling as if she is going to pass out. The patient has had 3 such episodes in the past 2 weeks, with symptoms occurring when she skips a meal. During the most recent episode, finger-stick glucose was 50 mg/dL. She was diagnosed with type 2 diabetes mellitus 3 years ago and initially treated with metformin monotherapy; glipizide was added 3 months ago due to inadequate glycemic control. The patient has no other medical conditions. Vital signs are within normal limits and physical examination shows no abnormalities. Hemoglobin A1c is 6.9%. The medication most likely responsible for this patient's current symptoms works by targeting which of the following?

- A. Intracellular mitochondrial enzymes
- B. Intracellular nuclear receptors
- C. Membrane ion channels
- D. Surface adenylate cyclase–coupled receptors
- E. Surface tyrosine kinase receptor

Submit

https://t.me/USMLEWorldStep1

A 46-year-old woman comes to the office due to frequent episodes of headache, nausea, sweating, and a feeling as if she is going to pass out. The patient has had 3 such episodes in the past 2 weeks, with symptoms occurring when she skips a meal. During the most recent episode, finger-stick glucose was 50 mg/dL. She was diagnosed with type 2 diabetes mellitus 3 years ago and initially treated with metformin monotherapy; glipizide was added 3 months ago due to inadequate glycemic control. The patient has no other medical conditions. Vital signs are within normal limits and physical examination shows no abnormalities. Hemoglobin A1c is 6.9%. The medication most likely responsible for this patient's current symptoms works by targeting which of the following?

- ✗ A. Intracellular mitochondrial enzymes (3%)
- B. Intracellular nuclear receptors (8%)
- ✓ C. Membrane ion channels (62%)
- D. Surface adenylate cyclase–coupled receptors (9%)
- E. Surface tyrosine kinase receptor (15%)

Incorrect
Correct answer
C

62%
Answered correctly

04 secs
Time Spent

2023
Version

Explanation

Noninsulin antidiabetic agents for type 2 diabetes mellitus		
Agent	**Mechanism of action**	**Adverse effects**
Insulin secretagogues • Sulfonylureas • Meglitinides	↑ Insulin secretion by inhibiting β-cell K_{ATP} channels	• Hypoglycemia • Weight gain
	Stimulate AMPK & inhibit mitochondrial	

https://t.me/USMLEWorldStep1

Noninsulin antidiabetic agents for type 2 diabetes mellitus		
Agent	**Mechanism of action**	**Adverse effects**
Insulin secretagogues • Sulfonylureas • Meglitinides	↑ Insulin secretion by inhibiting β-cell K_{ATP} channels	• Hypoglycemia • Weight gain
Biguanides • Metformin	Stimulate AMPK & inhibit mitochondrial gluconeogenesis, ↓ hepatic glucose production & ↑ peripheral glucose uptake	• Diarrhea • Lactic acidosis
Thiazolidinediones • Pioglitazone	Activate transcription regulator PPAR-γ, ↓ insulin resistance	• Fluid retention/heart failure • Weight gain
GLP-1 agonists • Exenatide • Liraglutide	↑ Glucose-dependent insulin secretion, ↓ glucagon secretion, delayed gastric emptying	• Pancreatitis • Weight loss
DPP4 inhibitors • Sitagliptin • Saxagliptin	↑ Endogenous GLP-1 & GIP levels	• Nasopharyngitis
SGLT-2 inhibitors • Canagliflozin • Dapagliflozin	↑ Renal glucose excretion	• Urinary tract infections • Hypotension
AMPK = AMP-activated protein kinase; **DPP4** = dipeptidyl peptidase-4; **GIP** = gastric inhibitory polypeptide; **GLP-1** = glucagon-like peptide-1; **K_{ATP}** = ATP-sensitive potassium; **PPAR-γ** = peroxisome proliferator–activated receptor γ; **SGLT-2** = sodium-glucose cotransporter-2.		

This patient has symptomatic hypoglycemia following initiation of a **sulfonylurea** medication (ie, glipizide) for diabetes mellitus. Sulfonylureas **inhibit** the ATP-sensitive **potassium channel** on the pancreatic beta cell

https://t.me/USMLEWorldStep1

This patient has symptomatic hypoglycemia following initiation of a **sulfonylurea** medication (ie, glipizide) for diabetes mellitus. Sulfonylureas **inhibit** the ATP-sensitive **potassium channel** on the pancreatic beta cell membrane, inducing depolarization with opening of L-type calcium channels (ie, increased Ca^{2+} influx), **stimulating insulin release**. Sulfonylurea-induced stimulation of beta cells is **independent of blood glucose** and occurs even when blood glucose levels are normal, increasing the risk for hypoglycemia.

The **risk for hypoglycemia** associated with sulfonylureas is increased in the setting of skipped meals (as in this patient), in excessively high medication doses, and with concurrent renal or hepatic disease (which decreases drug metabolism and clearance). Although hypoglycemia can occur with any sulfonylurea medication, the risk is highest with longer-acting sulfonylureas (eg, glyburide).

(Choice A) Metformin inhibits the mitochondrial enzymes required for gluconeogenesis, leading to decreased hepatic glucose production and lower circulating glucose levels. It also increases peripheral glucose uptake and improves insulin sensitivity by activating AMP-activated protein kinase. Metformin does not increase endogenous insulin secretion and therefore is not associated with hypoglycemia.

(Choice B) Thiazolidinediones (eg, pioglitazone) decrease insulin resistance by binding to peroxisome proliferator–activated receptor gamma, a transcriptional regulator of genes involved in glucose and lipid metabolism.

(Choice D) Glucagon-like polypeptide-1 (GLP-1) is secreted by the intestine in response to food intake and slows gastric emptying and increases glucose-dependent insulin release. GLP-1 agonists (eg, exenatide) act through cell surface receptors that are coupled with a G protein–adenylyl cyclase system. Because the effects of GLP-1 agonists are glucose dependent (eg, occur primarily in the presence of food), these medications are not typically associated with hypoglycemia.

(Choice E) Insulin acts by binding to a cell surface receptor consisting of 2 alpha and 2 beta subunits. The alpha subunits are located extracellularly and provide binding sites for insulin. The membrane-spanning beta subunits contain the intracellular tyrosine kinase domains.

Educational objective:
Sulfonylureas inhibit the ATP-sensitive potassium channel on the pancreatic beta cell membrane, inducing

https://t.me/USMLEWorldStep1

insulin release. Sulfonylurea-induced stimulation of beta cells is **independent of blood glucose** and occurs even when blood glucose levels are normal, increasing the risk for hypoglycemia.

The **risk for hypoglycemia** associated with sulfonylureas is increased in the setting of skipped meals (as in this patient), in excessively high medication doses, and with concurrent renal or hepatic disease (which decreases drug metabolism and clearance). Although hypoglycemia can occur with any sulfonylurea medication, the risk is highest with longer-acting sulfonylureas (eg, glyburide).

(Choice A) Metformin inhibits the mitochondrial enzymes required for gluconeogenesis, leading to decreased hepatic glucose production and lower circulating glucose levels. It also increases peripheral glucose uptake and improves insulin sensitivity by activating AMP-activated protein kinase. Metformin does not increase endogenous insulin secretion and therefore is not associated with hypoglycemia.

(Choice B) Thiazolidinediones (eg, pioglitazone) decrease insulin resistance by binding to peroxisome proliferator–activated receptor gamma, a transcriptional regulator of genes involved in glucose and lipid metabolism.

(Choice D) Glucagon-like polypeptide-1 (GLP-1) is secreted by the intestine in response to food intake and slows gastric emptying and increases glucose-dependent insulin release. GLP-1 agonists (eg, exenatide) act through cell surface receptors that are coupled with a G protein–adenylyl cyclase system. Because the effects of GLP-1 agonists are glucose dependent (eg, occur primarily in the presence of food), these medications are not typically associated with hypoglycemia.

(Choice E) Insulin acts by binding to a cell surface receptor consisting of 2 alpha and 2 beta subunits. The alpha subunits are located extracellularly and provide binding sites for insulin. The membrane-spanning beta subunits contain the intracellular tyrosine kinase domains.

Educational objective:
Sulfonylureas inhibit the ATP-sensitive potassium channel on the pancreatic beta cell membrane, inducing depolarization Ca^{2+} influx, and insulin release independent of blood glucose concentrations. Sulfonylureas can induce hypoglycemia because they stimulate insulin secretion even when blood glucose levels are normal.

Pharmacology Endocrine, Diabetes & Metabolism Diabetes mellitus

https://t.me/USMLEWorldStep1

A 34-year-old woman comes to the office with a 2-week history of palpitations, excessive sweating, and anxiety. The patient has obesity and has been unsuccessful in achieving significant weight loss with diet and exercise. In an attempt to lose weight, she has been taking excessive amounts of levothyroxine given to her by a friend. Pulse is 110/min. Physical examination shows sweaty palms and a soft, nontender, normal-sized thyroid gland. Laboratory evaluation reveals suppressed TSH and elevated free thyroxine (T4). Which of the following additional findings is most likely to be present in this patient?

	Radioactive iodine uptake	Serum thyroglobulin level	Total triiodothyronine (T3)
○ A.	↑	↑	↑
○ B.	↓	↑	↑
○ C.	↓	↓	↑
○ D.	↓	↓	Normal
○ E.	Normal	Normal	↑

Submit

https://t.me/USMLEWorldStep1

A 34-year-old woman comes to the office with a 2-week history of palpitations, excessive sweating, and anxiety. The patient has obesity and has been unsuccessful in achieving significant weight loss with diet and exercise. In an attempt to lose weight, she has been taking excessive amounts of levothyroxine given to her by a friend. Pulse is 110/min. Physical examination shows sweaty palms and a soft, nontender, normal-sized thyroid gland. Laboratory evaluation reveals suppressed TSH and elevated free thyroxine (T4). Which of the following additional findings is most likely to be present in this patient?

	Radioactive iodine uptake	Serum thyroglobulin level	Total triiodothyronine (T3)	
✗ A.	↑	↑	↑	(9%)
B.	↓	↑	↑	(17%)
✓ C.	↓	↓	↑	(44%)
D.	↓	↓	Normal	(10%)
E.	Normal	Normal	↑	(18%)

Incorrect
Correct answer
C

44%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

Differential diagnosis of thyrotoxicosis			
	Serum TSH	Serum thyroglobulin	Radioiodine uptake
Increased thyroid hormone production			

https://t.me/USMLEWorldStep1

Differential diagnosis of thyrotoxicosis			
	Serum TSH	**Serum thyroglobulin**	**Radioiodine uptake**
Increased thyroid hormone production (eg, Graves disease)	↓	↑	↑
Destruction of thyroid follicles (eg, subacute thyroiditis)	↓	↑↑	↓
Exogenous thyroid hormone	↓	↓	↓
Central hyperthyroidism (eg, pituitary adenoma)	↑	↑	↑

This patient has **exogenous thyrotoxicosis**, which can occur intentionally due to abuse of thyroid preparations (eg, **levothyroxine**, porcine thyroid extracts) or inadvertently due to errors in treatment of hypothyroidism. Symptoms resemble endogenous hyperthyroidism and include weight loss, tremor, heat intolerance, and tachycardia/palpitations.

In addition to elevated serum thyroxine (T4) and suppressed TSH, laboratory testing in exogenous thyrotoxicosis typically shows the following:

- **Radioactive iodine uptake** (RAIU): A radioiodine tracer is administered followed by scintigraphy of the thyroid gland; RAIU correlates with the organification of iodine and the synthesis of new thyroid hormone. In exogenous thyrotoxicosis, endogenous thyroid hormone synthesis is suppressed, so **RAIU is low**. If thyroid ultrasound is performed, Doppler shows decreased blood flow.
- **Thyroglobulin**: Thyroglobulin is a large glycoprotein in thyroid follicles that serves as a source of tyrosine residues for thyroid hormone synthesis. Small amounts of thyroglobulin are normally released with thyroid hormone, although greater quantities may be released in states of increased thyroid hormone synthesis or follicular destruction. In exogenous thyrotoxicosis, thyroid metabolic activity is low, and **serum thyroglobulin**

https://t.me/USMLEWorldStep1

This patient has **exogenous thyrotoxicosis**, which can occur intentionally due to abuse of thyroid preparations (eg, **levothyroxine**, porcine thyroid extracts) or inadvertently due to errors in treatment of hypothyroidism. Symptoms resemble endogenous hyperthyroidism and include weight loss, tremor, heat intolerance, and tachycardia/palpitations.

In addition to elevated serum thyroxine (T4) and suppressed TSH, laboratory testing in exogenous thyrotoxicosis typically shows the following:

- **Radioactive iodine uptake** (RAIU): A radioiodine tracer is administered followed by scintigraphy of the thyroid gland; RAIU correlates with the organification of iodine and the synthesis of new thyroid hormone. In exogenous thyrotoxicosis, endogenous thyroid hormone synthesis is suppressed, so **RAIU is low**. If thyroid ultrasound is performed, Doppler shows decreased blood flow.
- **Thyroglobulin**: Thyroglobulin is a large glycoprotein in thyroid follicles that serves as a source of tyrosine residues for thyroid hormone synthesis. Small amounts of thyroglobulin are normally released with thyroid hormone, although greater quantities may be released in states of increased thyroid hormone synthesis or follicular destruction. In exogenous thyrotoxicosis, thyroid metabolic activity is low, and **serum thyroglobulin is also low**.
- **Triiodothyronine (T3)**: T3 is derived primarily from T4 by deiodination in peripheral tissues, although small amounts are coreleased from the thyroid with T4. Exogenous levothyroxine is readily converted to T3, so T3 levels are also usually **elevated**.

(Choice A) Elevated RAIU, thyroglobulin, and T3 suggest increased metabolic activity in the thyroid (eg, Graves disease).

(Choice B) Elevated thyroglobulin and T3 with a suppressed RAIU suggest the destruction of thyroid follicles and the release of preformed thyroid hormone (eg, subacute thyroiditis).

(Choice D) Following thyroidectomy, patients with thyroid cancer are often treated with levothyroxine to achieve a subclinical hyperthyroid state; the suppressed TSH level avoids stimulation of residual malignant thyroid cells. RAIU and thyroglobulin are low because the thyroid is absent, but because the target hyperthyroid state is mild/subclinical, T3 is often normal or only slightly elevated.

https://t.me/USMLEWorldStep1

ultrasound is performed, Doppler shows decreased blood flow.

- **Thyroglobulin**: Thyroglobulin is a large glycoprotein in thyroid follicles that serves as a source of tyrosine residues for thyroid hormone synthesis. Small amounts of thyroglobulin are normally released with thyroid hormone, although greater quantities may be released in states of increased thyroid hormone synthesis or follicular destruction. In exogenous thyrotoxicosis, thyroid metabolic activity is low, and **serum thyroglobulin is also low**.
- **Triiodothyronine (T3)**: T3 is derived primarily from T4 by deiodination in peripheral tissues, although small amounts are coreleased from the thyroid with T4. Exogenous levothyroxine is readily converted to T3, so T3 levels are also usually **elevated**.

(Choice A) Elevated RAIU, thyroglobulin, and T3 suggest increased metabolic activity in the thyroid (eg, Graves disease).

(Choice B) Elevated thyroglobulin and T3 with a suppressed RAIU suggest the destruction of thyroid follicles and the release of preformed thyroid hormone (eg, subacute thyroiditis).

(Choice D) Following thyroidectomy, patients with thyroid cancer are often treated with levothyroxine to achieve a subclinical hyperthyroid state; the suppressed TSH level avoids stimulation of residual malignant thyroid cells. RAIU and thyroglobulin are low because the thyroid is absent, but because the target hyperthyroid state is mild/subclinical, T3 is often normal or only slightly elevated.

(Choice E) Thyroid hormone is carried in the circulation bound to plasma proteins, especially thyroid-binding globulin (TBG). TBG is elevated in hyperestrogenic states (eg, pregnancy, estrogen-based contraceptives); thyroid hormone production increases transiently to fill the increased number of binding sites, then activity (eg, RAIU, serum thyroglobulin) returns to normal. Total T3 and T4 are elevated, but free hormone levels are normal.

Educational objective:
In exogenous thyrotoxicosis, radioactive iodine uptake and serum thyroglobulin level are low, indicating suppression of endogenous thyroid metabolic activity. Serum T3 levels are often elevated.

Physiology	Endocrine, Diabetes & Metabolism	Hyperthyroidism
Subject	System	Topic

https://t.me/USMLEWorldStep1

This patient has **exogenous thyrotoxicosis**, which can occur intentionally due to abuse of thyroid preparations (eg, **levothyroxine**, porcine thyroid extracts) or inadvertently due to errors in treatment of hypothyroidism.

Sympt

tachyc

In add

typical

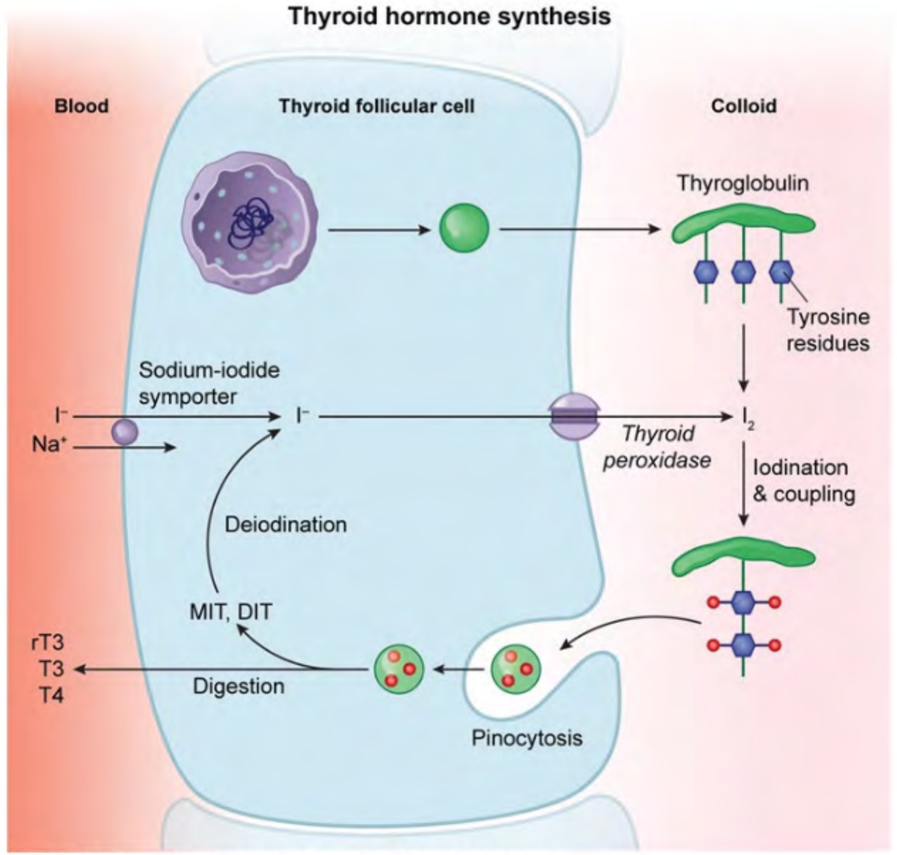
- **R** th e u
- **T** re h fo **is**
- **T** a le

(Choi diseas

(Choi the rel

(Choi subcli RAIU and thyroglobulin are low because the thyroid is absent, but because the target hyperthyroid state is mild/subclinical, T3 is often normal or only slightly elevated.

Exhibit Display



DIT = diiodotyrosine; **rT3** = reverse triiodothyronine; **T3** = triiodothyronine; **T4** = thyroxine; **MIT** = monoiodotyrosine.

©UWorld

Zoom In Zoom Out Reset New | Existing My Notebook

https://t.me/USMLEWorldStep1

ultrasound is performed, Doppler shows decreased blood flow.

- **Thyroglobulin**: Thyroglobulin is a large glycoprotein in thyroid follicles that serves as a source of tyrosine re
h
fo
is
- **T**
a
le

(Choi
diseas

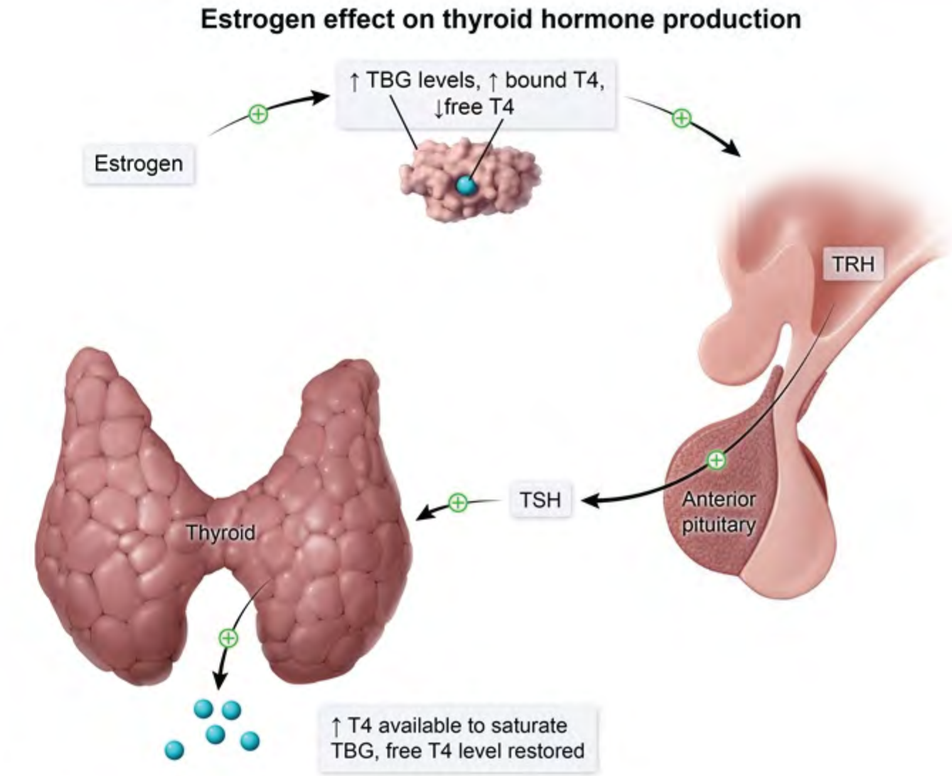
(Choi
the rel

(Choi
subcli
RAIU
mild/s

(Choi
globuli
hormo
serum

Educa
In exo
suppre

Exhibit Display



TBG = thyroxine-binding globulin.
©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Physiology	Endocrine, Diabetes & Metabolism	Hyperthyroidism
Subject	System	Topic

https://t.me/USMLEWorldStep1

A 21-year-old man comes to clinic for a routine health maintenance visit. During testicular examination, he is found to have a single testis in the scrotum. Laboratory evaluation shows an elevated serum FSH level and a normal serum LH level. Production of which of the following substances is most likely decreased in this patient?

- A. Dehydroepiandrosterone
- B. Dihydrotestosterone
- C. GnRH
- D. Inhibin B
- E. Testosterone

Submit

https://t.me/USMLEWorldStep1

A 21-year-old man comes to clinic for a routine health maintenance visit. During testicular examination, he is found to have a single testis in the scrotum. Laboratory evaluation shows an elevated serum FSH level and a normal serum LH level. Production of which of the following substances is most likely decreased in this patient?

- A. Dehydroepiandrosterone
- ✗ B. Dihydrotestosterone
- C. GnRH
- ✓ D. Inhibin B
- E. Testosterone

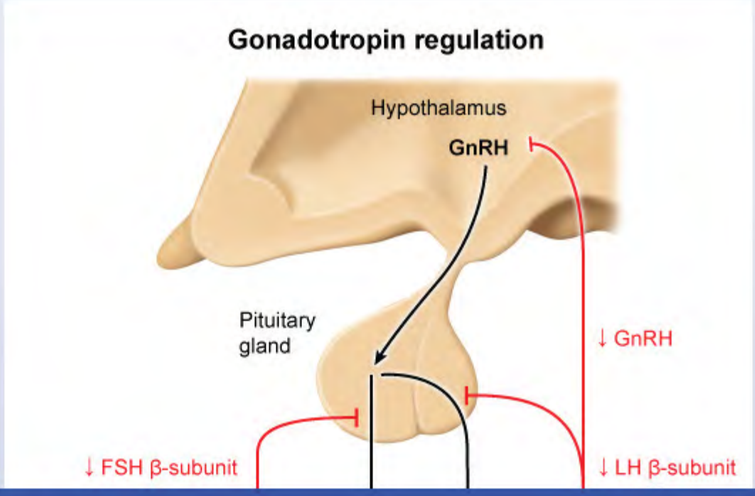
Incorrect
Correct answer
D

Collecting Statistics

03 secs
Time Spent

2023
Version

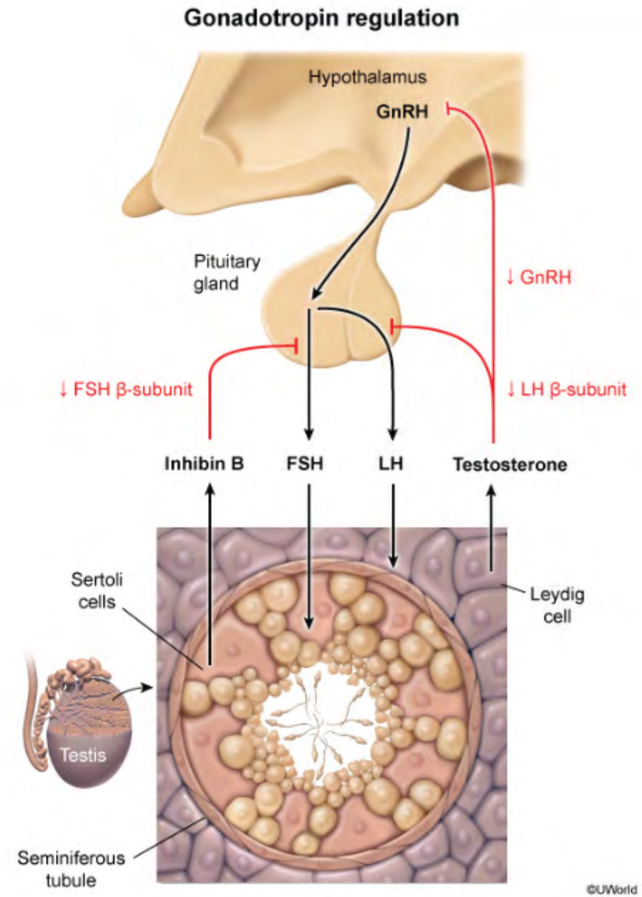
Explanation



https://t.me/USMLEWorldStep1

A 21-year-old man comes to clinic for a routine health maintenance visit. During testicular examination, he is found to hav
serum

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

↓ FSH β-subunit
↓ LH β-subunit

https://t.me/USMLEWorldStep1



©UWorld

Normal functioning of the hypothalamic-pituitary-gonadal axis involves pulsatile secretion of GnRH from the hypothalamus, which stimulates the release of FSH and LH from the gonadotrophs of the anterior pituitary. LH triggers the release of testosterone from the Leydig cells of the testes; FSH stimulates the release of inhibin B from the Sertoli cells of the testes. Testosterone has a negative feedback effect on LH and GnRH secretion, while **inhibin B suppresses FSH secretion**.

Sertoli cells within the seminiferous tubules are **temperature sensitive** and prone to atrophy from heat damage when located outside of the scrotum, which is at a relatively lower temperature than the body's core. Therefore, when there is an **undescended testicle** (as in this patient with only 1 scrotal testicle) Sertoli cell mass is reduced and circulating levels of **inhibin B** are **low**. In turn, the lack of negative feedback from inhibin B on FSH production results in **elevated FSH** levels.

(Choice A) Although dehydroepiandrosterone (DHEA) is a precursor to testosterone, the testicles only release a small amount of DHEA into the circulation. Systemic levels of DHEA are derived primarily from the adrenal glands.

(Choices B, C, and E) In contrast to heat-sensitive Sertoli cells, Leydig cell function is not significantly affected by increased temperature, so testosterone, dihydrotestosterone, and LH levels are usually normal in cryptorchidism. In addition, this patient's normal LH level is indicative of normal (not decreased) GnRH activity.

Educational objective:
Inhibin B, which is produced by heat-sensitive Sertoli cells, is a physiologic inhibitor of FSH secretion. In patients with cryptorchidism, atrophy of Sertoli cells results in decreased inhibin B and, in turn, elevated FSH. In contrast, Leydig cell function is not significantly affected, so testosterone and LH levels are typically normal in these patients.

References

- Inhibin B in healthy and cryptorchid boys.

Physiology	Endocrine, Diabetes & Metabolism	Cryptorchidism
Subject	System	Topic

Copyright © UWorld. All rights reserved.

https://t.me/USMLEWorldStep1

A 42-year-old woman comes to the physician for a routine check-up. She has no current complaints and no significant past medical history. On physical examination, the physician notes lesions on her eyelids that are pictured below.



Which of the following is the best next step in the management of this patient?

- A. ECG and serum cardiac enzymes
- B. Serum lipids and blood glucose level
- C. Liver function tests and abdominal ultrasonography
- D. Complete blood count and stool guaiac test
- E. Slit lamp exam and ophthalmoscopy

https://t.me/USMLEWorldStep1

pictured below.



Which of the following is the best next step in the management of this patient?

- A. ECG and serum cardiac enzymes
- B. Serum lipids and blood glucose level
- C. Liver function tests and abdominal ultrasonography
- D. Complete blood count and stool guaiac test
- E. Slit lamp exam and ophthalmoscopy
- F. Lesion biopsy and surgeon referral

Submit

https://t.me/USMLEWorldStep1

pictured below:



Which of the following is the best next step in the management of this patient?

- ✗ A. ECG and serum cardiac enzymes (0%)
- ✓ B. Serum lipids and blood glucose level (93%)
- C. Liver function tests and abdominal ultrasonography (3%)
- D. Complete blood count and stool guaiac test (0%)
- E. Slit lamp exam and ophthalmoscopy (0%)
- F. Lesion biopsy and surgeon referral (0%)

Incorrect
Correct answer

93%

15 secs

2023

https://t.me/USMLEWorldStep1

Explanation

The lesion pictured is a xanthelasma, a type of xanthoma usually found on the medial eyelids. Hyperlipidemia and/or dyslipidemia can result in xanthomas (including xanthelasmas). Xanthelasmas are dermal accumulations of benign-appearing macrophages with abundant, finely vacuolated (foamy) cytoplasm containing cholesterol (free and esterified), phospholipids, and triglycerides. Due in part to insulin resistance promoting increased VLDL production, diabetics may develop a secondary Type IV or V hyperlipidemia (increased VLDL, chylomicrons) and/or a secondary diabetic dyslipidemia with elevated LDL cholesterol and low HDL cholesterol. Thus, in order to determine the type of this patient's lipid disorder and to rule out underlying diabetes, her serum lipids and blood glucose should be measured.

(Choice A) Although this patient may be at increased risk for coronary artery disease due to hyperlipidemia or dyslipidemia, she does not currently have symptoms of myocardial infarction. Her current management should be focused on treating her lipid disorder.

(Choice C) The first step in managing this patient is to establish what type of lipid abnormality she has based upon her serum lipid levels and lipoprotein profile. If the results are consistent with an obstructive liver and/or biliary system lesion producing cholestasis and hypercholesterolemia, then liver function tests and abdominal ultrasonography may be warranted.

(Choice D) A CBC and stool guaiac test are performed when searching for occult GI bleeding.

(Choice E) Slit lamp examination and funduscopy could reveal ocular findings associated with this patient's lipid disorder, such as a corneal arcus (lipid deposit) or lipemia retinalis. However, a serum lipid profile should be obtained next in order to establish the type of hyperlipidemia or dyslipidemia in this patient.

(Choice F) Xanthelasmas are usually diagnosed based on clinical appearance. Biopsy is not required. Treatment is primarily medical and directed at the underlying lipid abnormality. Surgical excision is not medically necessary, but may be undertaken electively for cosmetic reasons.

Educational objective:
Xanthelasmas, a type of xanthoma, are yellowish macules/papules found on the medial eyelids. They are dermal

https://t.me/USMLEWorldStep1

The lesion pictured is a xanthelasma, a type of xanthoma usually found on the medial eyelids. Hyperlipidemia and/or dyslipidemia can result in xanthomas (including xanthelasmas). Xanthelasmas are dermal accumulations of benign-appearing macrophages with abundant, finely vacuolated (foamy) cytoplasm containing cholesterol (free and esterified), phospholipids, and triglycerides. Due in part to insulin resistance promoting increased VLDL production, diabetics may develop a secondary Type IV or V hyperlipidemia (increased VLDL, chylomicrons) and/or a secondary diabetic dyslipidemia with elevated LDL cholesterol and low HDL cholesterol. Thus, in order to determine the type of this patient's lipid disorder and to rule out underlying diabetes, her serum lipids and blood glucose should be measured.

(Choice A) Although this patient may be at increased risk for coronary artery disease due to hyperlipidemia or dyslipidemia, she does not currently have symptoms of myocardial infarction. Her current management should be focused on treating her lipid disorder.

(Choice C) The first step in managing this patient is to establish what type of lipid abnormality she has based upon her serum lipid levels and lipoprotein profile. If the results are consistent with an obstructive liver and/or biliary system lesion producing cholestasis and hypercholesterolemia, then liver function tests and abdominal ultrasonography may be warranted.

(Choice D) A CBC and stool guaiac test are performed when searching for occult GI bleeding.

(Choice E) Slit lamp examination and funduscopy could reveal ocular findings associated with this patient's lipid disorder, such as a corneal arcus (lipid deposit) or lipemia retinalis. However, a serum lipid profile should be obtained next in order to establish the type of hyperlipidemia or dyslipidemia in this patient.

(Choice F) Xanthelasmas are usually diagnosed based on clinical appearance. Biopsy is not required. Treatment is primarily medical and directed at the underlying lipid abnormality. Surgical excision is not medically necessary, but may be undertaken electively for cosmetic reasons.

Educational objective:
Xanthelasmas, a type of xanthoma, are yellowish macules/papules found on the medial eyelids. They are dermal accumulations of macrophages containing cholesterol and triglycerides, and are generally associated with a primary or secondary hyperlipidemia or dyslipidemia. An LDL receptor abnormality is the most common cause.

https://t.me/USMLEWorldStep1

A 52-year-old, post-menopausal woman comes to the office for a follow-up appointment. Six months ago, the patient was evaluated for recurrent, brief episodes of excessive warmth and sweating, which were interfering with her usual activities. Thyroid hormone levels were normal, and the patient was subsequently diagnosed with menopausal hot flashes. Treatment with estrogen-containing hormone replacement therapy was begun with significant symptom improvement. She has no other medical conditions and takes no other medications. Which of the following most likely occurred in this patient as a result of her medication use?

- A. Decreased conversion of T4 to T3
- B. Decreased thyroid iodine uptake
- C. Decreased TSH level
- D. Increased free T3 level
- E. Increased total T4 level

Submit

https://t.me/USMLEWorldStep1

A 52-year-old, post-menopausal woman comes to the office for a follow-up appointment. Six months ago, the patient was evaluated for recurrent, brief episodes of excessive warmth and sweating, which were interfering with her usual activities. Thyroid hormone levels were normal, and the patient was subsequently diagnosed with menopausal hot flashes. Treatment with estrogen-containing hormone replacement therapy was begun with significant symptom improvement. She has no other medical conditions and takes no other medications. Which of the following most likely occurred in this patient as a result of her medication use?

- A. Decreased conversion of T4 to T3 (18%)
- ✗ B. Decreased thyroid iodine uptake (3%)
- C. Decreased TSH level (31%)
- D. Increased free T3 level (6%)
- ✓ E. Increased total T4 level (39%)

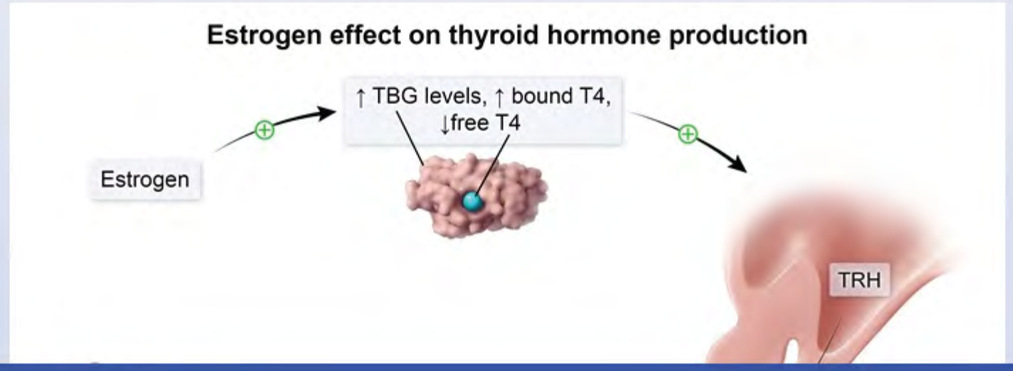
Incorrect
Correct answer
E

39%
Answered correctly

03 secs
Time Spent

2023
Version

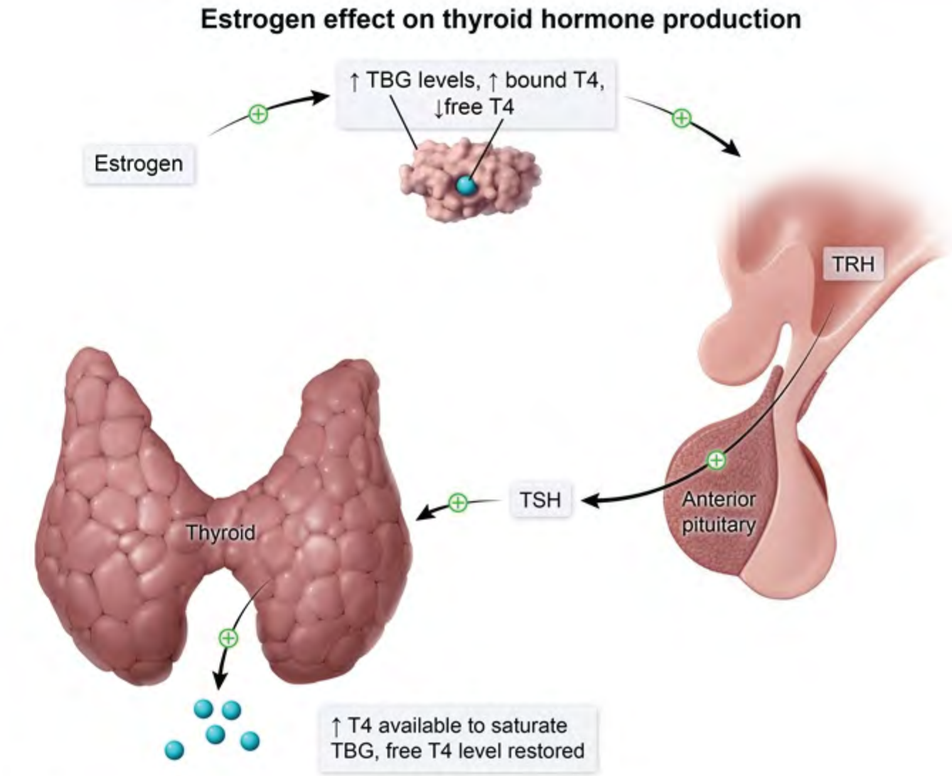
Explanation



https://t.me/USMLEWorldStep1

A 52-year-old, post-menopausal woman comes to the office for a follow-up appointment. Six months ago, the patien
her us
menop
signifi
the fol

Exhibit Display



TBG = thyroxine-binding globulin.

©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

©UWorld

Circulating thyroid hormone consists of 2 fractions: an inert **protein-bound** fraction and a **free fraction** that is available to enter target cells via a carrier-mediated mechanism. More than 99% of circulating thyroid hormone is bound to plasma proteins, creating a large circulating reservoir of thyroid hormone. **Thyroxine-binding globulin** (TBG) accounts for approximately 70% of thyroid hormone binding with an additional share bound by albumin and transthyretin.

An **increase in estrogen activity** (eg, pregnancy, oral contraceptive use, postmenopausal hormone replacement therapy) **raises circulating TBG levels**, causing a corresponding reduction in free T4 and T3 levels. In patients with a normal hypothalamic-pituitary-thyroid axis, this reduction will result in a transient increase in TSH, leading to increased thyroid hormone production until the additional TBG becomes saturated with thyroid hormone and free T4 and T3 levels are restored (ie, patients remain **euthyroid**). Therefore, an increase in the TBG level leads to an **increase in total T4** and T3 (bound plus free fractions).

(Choice A) Estrogen does not affect the peripheral conversion of T4 to T3. Medications that decrease the peripheral conversion of T4 to T3 include propylthiouracil, glucocorticoids, and nonselective beta blockers.

(Choices B and C) Thyroid iodine uptake *increases* transiently due to the temporary *rise* in TSH that occurs with increased TBG synthesis. However, iodine uptake normalizes once the newly synthesized TBG becomes saturated with thyroid hormone and TSH returns to normal.

(Choice D) Increased circulating TBG levels cause a transient *drop* in free T4 and T3 levels as the existing pool of thyroid hormone becomes more protein-bound. However, free T4 and T3 levels quickly normalize as the thyroid synthesizes an appropriate quantity of new thyroid hormone to saturate the additional TBG.

Educational objective:
An increase in estrogen activity, as seen in pregnancy or postmenopausal estrogen replacement therapy, increases the level of thyroxine-binding globulin. This leads to an increase in total thyroid hormone levels, but feedback control maintains normal levels of free (biologically active) thyroid hormone.

Pharmacology	Endocrine, Diabetes & Metabolism	Menopause
Subject	System	Topic

https://t.me/USMLEWorldStep1

A 25-year-old man comes to the physician because he and his wife have been unable to conceive for the last 2 years. They have no children. Infertility evaluation is begun, and laboratory studies show a low sperm count. A more thorough evaluation elucidates a rare genetic abnormality that leads to permanently inactive FSH receptors. Which of the following substances is most likely decreased in this patient?

- A. FSH
- B. LH
- C. Inhibin B
- D. Testosterone
- E. DHEA

Submit

https://t.me/USMLEWorldStep1

A 25-year-old man comes to the physician because he and his wife have been unable to conceive for the last 2 years. They have no children. Infertility evaluation is begun, and laboratory studies show a low sperm count. A more thorough evaluation elucidates a rare genetic abnormality that leads to permanently inactive FSH receptors. Which of the following substances is most likely decreased in this patient?

- A. FSH (1%)
- ✕ B. LH (2%)
- ✓ C. Inhibin B (79%)
- D. Testosterone (12%)
- E. DHEA (4%)

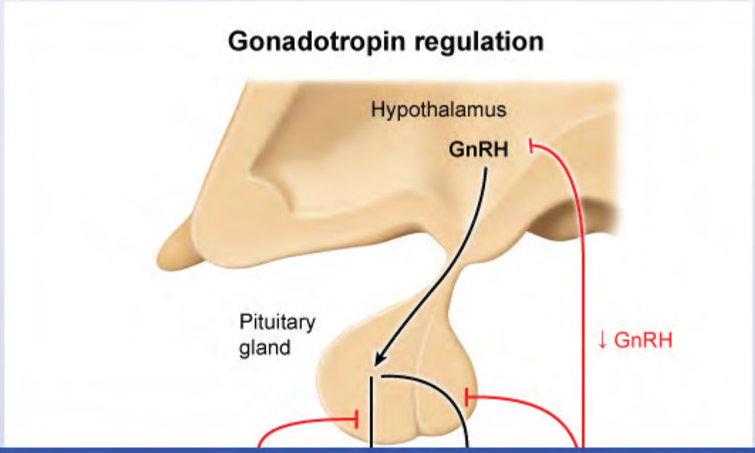
Incorrect
Correct answer
C

79%
Answered correctly

03 secs
Time Spent

2023
Version

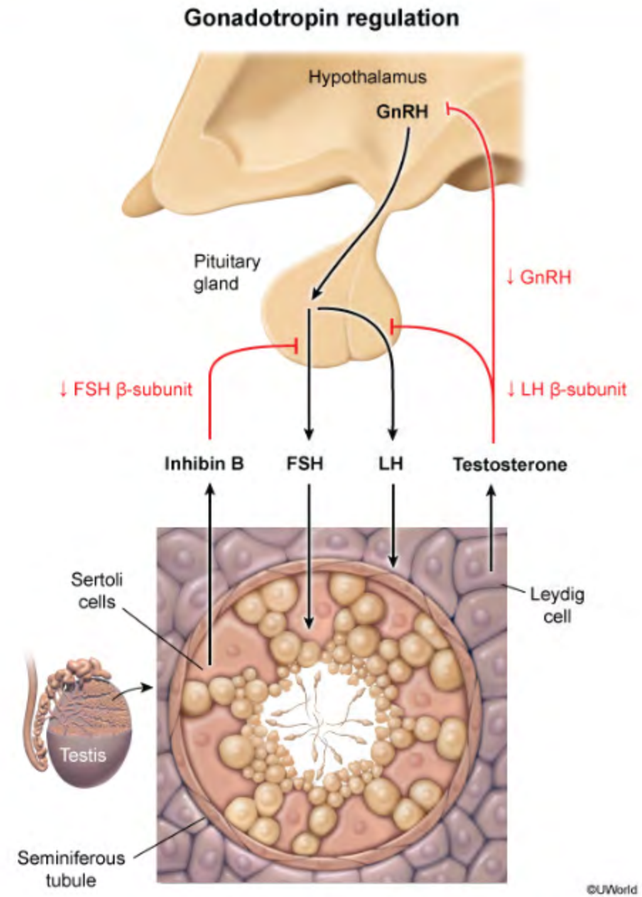
Explanation



https://t.me/USMLEWorldStep1

A 25-year-old man comes to the physician because he and his wife have been unable to conceive for the last 2 years.
more t
Which

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1



©UWorld

Pulsatile secretion of gonadotrophin-releasing hormone from the hypothalamus stimulates the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the gonadotroph cells in the anterior pituitary. LH stimulates the release of testosterone from the Leydig cells in the interstitium of the testicles, and FSH stimulates the release of inhibin B from the Sertoli cells in the seminiferous tubules of the testicles. Testosterone and inhibin B induce negative feedback on LH and FSH production, respectively.

FSH also stimulates the Sertoli cells to produce androgen-binding protein locally, within the seminiferous tubules. This androgen-binding protein is responsible for the high local testosterone concentration and is different from sex hormone-binding globulin, which is found in the blood. High local levels of testosterone and FSH are necessary for spermatogenesis. Defective FSH receptors will prevent spermatogenesis and cause low inhibin B levels, because FSH is responsible for both spermatogenesis and inhibin B production.

(Choice A) FSH levels will be high in patients with FSH receptor defects because there is no negative feedback from inhibin B; inhibin B cannot be produced without proper functioning of the FSH pathway.

(Choices B and D) LH and testosterone levels are likely to be normal in this patient because FSH does not play a role in either LH or testosterone feedback. Since the FSH receptor defect is isolated, this patient will have normal testosterone and LH levels.

(Choice E) The circulating levels of other androgens such as DHEA, DHEAS, and androstenedione are also not affected by FSH.

Educational objective:
LH stimulates the release of testosterone from the Leydig cells of the testes; FSH stimulates the release of inhibin B from the Sertoli cells in the seminiferous tubules. Testosterone and inhibin B induce negative feedback on LH and FSH production, respectively.

Physiology	Endocrine, Diabetes & Metabolism	Infertility
Subject	System	Topic

Copyright © UWorld. All rights reserved.

https://t.me/USMLEWorldStep1

A 34-year-old woman experiences nausea, abdominal pain, and dizziness after undergoing open reduction and internal fixation of a femur fracture. One year ago, she was diagnosed with systemic lupus erythematosus with significant renal involvement, and she has since been on chronic glucocorticoid therapy with prednisone. The patient was maintained on her usual daily dose of prednisone throughout the perioperative period. Blood pressure is 90/60 mm Hg and pulse is 120/min. Compared to the normal physiologic response to surgery, this patient most likely has which of the following patterns of hypothalamic-pituitary-adrenal axis activity?

	Corticotropin-releasing hormone	ACTH	Cortisol
○ A.	Increased	Increased	Increased
○ B.	Increased	Increased	Decreased
○ C.	Increased	Decreased	Decreased
○ D.	Decreased	Decreased	Increased
○ E.	Decreased	Decreased	Decreased

Submit

https://t.me/USMLEWorldStep1

A 34-year-old woman experiences nausea, abdominal pain, and dizziness after undergoing open reduction and internal fixation of a femur fracture. One year ago, she was diagnosed with systemic lupus erythematosus with significant renal involvement, and she has since been on chronic glucocorticoid therapy with prednisone. The patient was maintained on her usual daily dose of prednisone throughout the perioperative period. Blood pressure is 90/60 mm Hg and pulse is 120/min. Compared to the normal physiologic response to surgery, this patient most likely has which of the following patterns of hypothalamic-pituitary-adrenal axis activity?

		Corticotropin-releasing hormone	ACTH	Cortisol	
	A.	Increased	Increased	Increased	(1%)
✗	B.	Increased	Increased	Decreased	(12%)
	C.	Increased	Decreased	Decreased	(6%)
	D.	Decreased	Decreased	Increased	(22%)
✓	E.	Decreased	Decreased	Decreased	(56%)

Incorrect
Correct answer
E

56%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

This patient is suffering from **acute adrenal insufficiency (adrenal crisis)** due to suppression of the hypothalamic-pituitary-adrenal (HPA) axis by long-term glucocorticoid therapy. Glucocorticoids suppress the synthesis and release of corticotropin-releasing hormone (CRH) from the hypothalamus and also block its ACTH stimulatory effect on the anterior pituitary. Long-term suppression leads to **atrophy** of hypothalamic CRH-releasing neurons, pituitary corticotrophic cells, and the adrenal zona reticularis (androgen- producing inner zone) and zona fasciculata (cortisol-producing middle zone).

https://t.me/USMLEWorldStep1

Explanation

This patient is suffering from **acute adrenal insufficiency (adrenal crisis)** due to suppression of the hypothalamic-pituitary-adrenal (HPA) axis by long-term glucocorticoid therapy. Glucocorticoids suppress the synthesis and release of corticotropin-releasing hormone (CRH) from the hypothalamus and also block its ACTH stimulatory effect on the anterior pituitary. Long-term suppression leads to **atrophy** of hypothalamic CRH-releasing neurons, pituitary corticotrophic cells, and the adrenal zona reticularis (androgen- producing inner zone) and zona fasciculata (cortisol-producing middle zone).

Chronic glucocorticoid use is characterized by **low** CRH, ACTH, and cortisol levels that **cannot rise** in response to stressful situations (eg, infections, surgery) **(Choice A)**. This lack of a stress response can result in **relative glucocorticoid deficiency** even when the patient's baseline glucocorticoid regimen is maintained. Because glucocorticoids help maintain normal vascular tone (eg, by increasing norepinephrine, renin, and angiotensin vasoconstrictive activity), glucocorticoid deficiency can precipitate **hypotension/shock**. In such cases, a higher **stress dose** is needed to compensate for the increased physiologic demands and prevent the development of adrenal crisis.

(Choice B) Increased levels of CRH and ACTH with decreased cortisol suggest primary adrenal insufficiency, as may be seen in autoimmune adrenalitis or bilateral adrenal hemorrhage/infarction. These patients will also have mineralocorticoid deficiency and are at very high risk for adrenal crisis.

(Choice C) Increased CRH with decreased levels of ACTH and cortisol suggest a pituitary disorder. ACTH is secreted by corticotroph cells of the anterior pituitary; damage to the pituitary by a tumor, infarction, or infection can cause decreased release of ACTH, which in turn leads to decreased cortisol production.

(Choice D) Excessive cortisol production from an autonomous adrenal adenoma suppresses CRH and ACTH production by the hypothalamus and pituitary, respectively.

Educational objective:
Suppression of the hypothalamus-pituitary-adrenal axis by glucocorticoid therapy is the most common cause of adrenal insufficiency. In these patients, adrenal crisis can be precipitated by stressful situations (eg, infections,

https://t.me/USMLEWorldStep1

This patient is suffering from **acute adrenal insufficiency (adrenal crisis)** due to suppression of the hypothalamic-pituitary-adrenal (HPA) axis by long-term glucocorticoid therapy. Glucocorticoids suppress the synthesis and release of corticotropin-releasing hormone (CRH) from the hypothalamus and also block its ACTH stimulatory effect on the anterior pituitary. Long-term suppression leads to **atrophy** of hypothalamic CRH-releasing neurons, pituitary corticotrophic cells, and the adrenal zona reticularis (androgen- producing inner zone) and zona fasciculata (cortisol-producing middle zone).

Chronic glucocorticoid use is characterized by **low** CRH, ACTH, and cortisol levels that **cannot rise** in response to stressful situations (eg, infections, surgery) **(Choice A)**. This lack of a stress response can result in **relative glucocorticoid deficiency** even when the patient's baseline glucocorticoid regimen is maintained. Because glucocorticoids help maintain normal vascular tone (eg, by increasing norepinephrine, renin, and angiotensin vasoconstrictive activity), glucocorticoid deficiency can precipitate **hypotension/shock**. In such cases, a higher **stress dose** is needed to compensate for the increased physiologic demands and prevent the development of adrenal crisis.

(Choice B) Increased levels of CRH and ACTH with decreased cortisol suggest primary adrenal insufficiency, as may be seen in autoimmune adrenalitis or bilateral adrenal hemorrhage/infarction. These patients will also have mineralocorticoid deficiency and are at very high risk for adrenal crisis.

(Choice C) Increased CRH with decreased levels of ACTH and cortisol suggest a pituitary disorder. ACTH is secreted by corticotroph cells of the anterior pituitary; damage to the pituitary by a tumor, infarction, or infection can cause decreased release of ACTH, which in turn leads to decreased cortisol production.

(Choice D) Excessive cortisol production from an autonomous adrenal adenoma suppresses CRH and ACTH production by the hypothalamus and pituitary, respectively.

Educational objective:
Suppression of the hypothalamus-pituitary-adrenal axis by glucocorticoid therapy is the most common cause of adrenal insufficiency. In these patients, adrenal crisis can be precipitated by stressful situations (eg, infections, surgery) if the glucocorticoid dose is not increased appropriately.

References

- Extensive expertise in endocrinology. Adrenal crisis.

https://t.me/USMLEWorldStep1

This patient is suffering from **acute adrenal insufficiency (adrenal crisis)** due to suppression of the hypothalamic-pituitary-adrenal (HPA) axis by long-term glucocorticoid therapy. Glucocorticoids suppress the synthe
stimula
neuron
fascicu

Chron
stress
gluco
glucoc
vasoc
stress
adrena

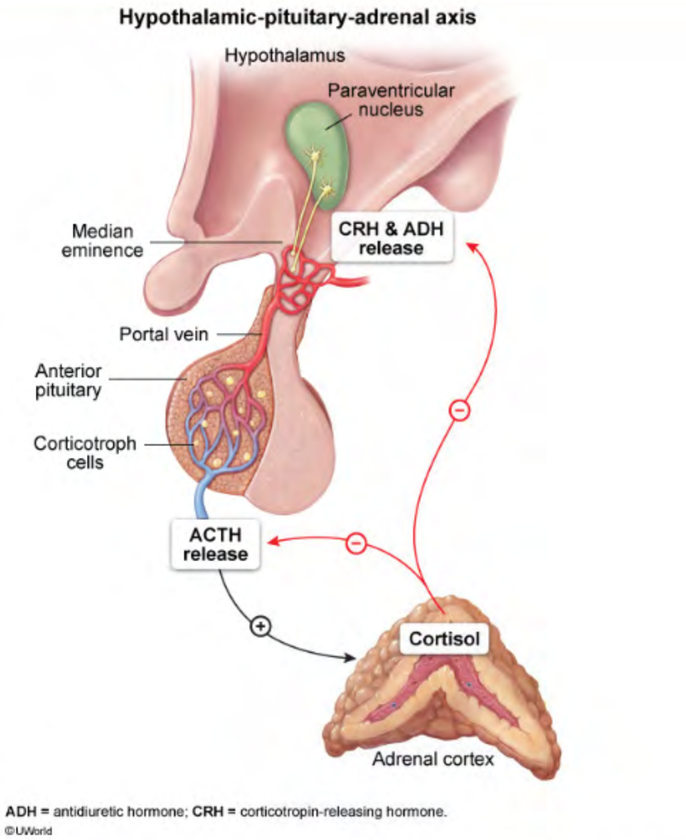
(Choi
may b
minera

(Choi
secret
cause

(Choi
produc

Educa
Suppr
adrena
surgery) if the glucocorticoid dose is not increased appropriately.

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

References

- Extensive expertise in endocrinology. Adrenal crisis.

https://t.me/USMLEWorldStep1

A 52-year-old man comes to the office due to easy bruisibility and muscle weakness. Medical history is unremarkable, but the patient has smoked a pack of cigarettes daily for 30 years. Blood pressure is 160/110 mm Hg, and pulse is 80/min. BMI is 29 kg/m^2. Physical examination shows facial plethora, slight centripetal distribution of body fat, diffuse skin pigmentation, and bilateral peripheral edema. Fasting blood glucose is 160 mg/dL and creatinine is 1.2 mg/dL. Chest x-ray reveals a lung mass. Which of the following is the most likely cause of this patient's elevated blood pressure?

- A. Activation of renal mineralocorticoid receptors
- B. Elevated plasma catecholamine level
- C. Impaired glomerular filtration of sodium and water
- D. Marked urinary loss of albumin
- E. Renal resistance to antidiuretic hormone

Submit

https://t.me/USMLEWorldStep1

A 52-year-old man comes to the office due to easy bruisibility and muscle weakness. Medical history is unremarkable, but the patient has smoked a pack of cigarettes daily for 30 years. Blood pressure is 160/110 mm Hg, and pulse is 80/min. BMI is 29 kg/m^2. Physical examination shows facial plethora, slight centripetal distribution of body fat, diffuse skin pigmentation, and bilateral peripheral edema. Fasting blood glucose is 160 mg/dL and creatinine is 1.2 mg/dL. Chest x-ray reveals a lung mass. Which of the following is the most likely cause of this patient's elevated blood pressure?

- ✓ A. Activation of renal mineralocorticoid receptors (73%)
- ✗ B. Elevated plasma catecholamine level (18%)
- C. Impaired glomerular filtration of sodium and water (4%)
- D. Marked urinary loss of albumin (1%)
- E. Renal resistance to antidiuretic hormone (2%)

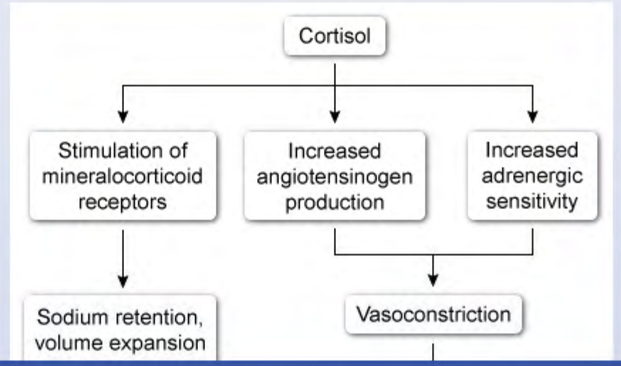
Incorrect
Correct answer
A

73%
Answered correctly

03 secs
Time Spent

2023
Version

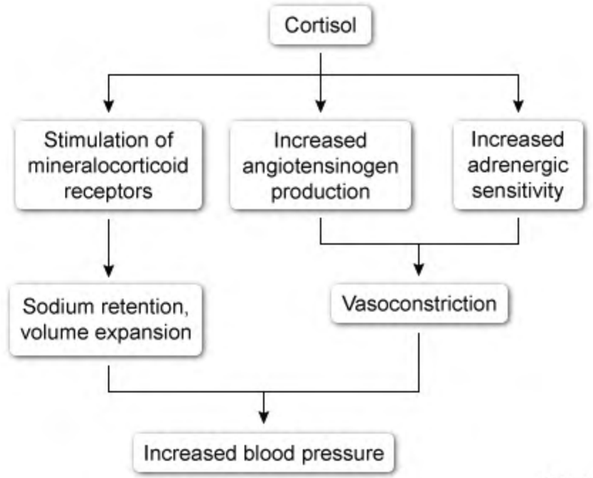
Explanation



https://t.me/USMLEWorldStep1

A 52-year-old man comes to the office due to easy bruisibility and muscle weakness. Medical history is unrem
Hg, ar
distrib
mg/dL
cause

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Sodium retention, volume expansion
Vasoconstriction

https://t.me/USMLEWorldStep1

This patient has **Cushing syndrome** (CS) presenting with hypertension, facial plethora, easy bruising, centripetal obesity (ie, trunk, abdomen), and hyperglycemia. In light of the associated hyperpigmentation (due to the cosecretion of ACTH and melanocyte-stimulating hormone) and lung mass, this is likely due to an **ACTH-secreting small cell lung cancer**. Paraneoplastic CS often develops rapidly, and the characteristic facial features may not be present at the time of diagnosis.

High levels of cortisol, as seen in patients with CS, frequently cause **hypertension** due to a combination of the following:

- Increased peripheral vascular sensitivity to adrenergic stimuli
- Increased hepatic production of renin substrate (angiotensinogen)
- Activation of renal tubular mineralocorticoid receptors

Activation of **renal mineralocorticoid receptors** usually occurs in patients with **severe hypercortisolism**, which is often due to ectopic ACTH secretion. This receptor activation induces sodium reabsorption and potassium wasting in the renal collecting tubules.

(Choice B) Elevated plasma catecholamine levels occur with pheochromocytoma. Hypertension is common, although it is often severe (eg, systolic blood pressure >180 mm Hg), paroxysmal, and associated with tachypalpitations. However, hyperpigmentation and edema would not be expected.

(Choice C) Impaired filtration of sodium and water is a major cause of hypertension and peripheral edema in patients with glomerulonephritis and/or other causes of kidney injury; in such cases, creatinine would be elevated. Given this patient's hyperpigmentation, hyperglycemia, and lung mass, CS is more likely.

(Choice D) Marked urinary loss of albumin and other proteins is characteristic of nephrotic syndrome. Peripheral edema is usually present due to reduced intravascular oncotic pressure, but hypertension is unusual unless the glomerular filtration rate is impaired (eg, elevated creatinine). Also, hyperpigmentation is not seen.

(Choice E) Renal resistance to antidiuretic hormone occurs in nephrogenic diabetes insipidus. Patients are either euvolemic or hypovolemic (if they cannot obtain drinking water as needed) and do not have hypertension or peripheral edema.

Educational objective:

https://t.me/USMLEWorldStep1

following:

- Increased peripheral vascular sensitivity to adrenergic stimuli
- Increased hepatic production of renin substrate (angiotensinogen)
- Activation of renal tubular mineralocorticoid receptors

Activation of **renal mineralocorticoid receptors** usually occurs in patients with **severe hypercortisolism**, which is often due to ectopic ACTH secretion. This receptor activation induces sodium reabsorption and potassium wasting in the renal collecting tubules.

(Choice B) Elevated plasma catecholamine levels occur with pheochromocytoma. Hypertension is common, although it is often severe (eg, systolic blood pressure >180 mm Hg), paroxysmal, and associated with tachypalpitations. However, hyperpigmentation and edema would not be expected.

(Choice C) Impaired filtration of sodium and water is a major cause of hypertension and peripheral edema in patients with glomerulonephritis and/or other causes of kidney injury; in such cases, creatinine would be elevated. Given this patient's hyperpigmentation, hyperglycemia, and lung mass, CS is more likely.

(Choice D) Marked urinary loss of albumin and other proteins is characteristic of nephrotic syndrome. Peripheral edema is usually present due to reduced intravascular oncotic pressure, but hypertension is unusual unless the glomerular filtration rate is impaired (eg, elevated creatinine). Also, hyperpigmentation is not seen.

(Choice E) Renal resistance to antidiuretic hormone occurs in nephrogenic diabetes insipidus. Patients are either euvolemic or hypovolemic (if they cannot obtain drinking water as needed) and do not have hypertension or peripheral edema.

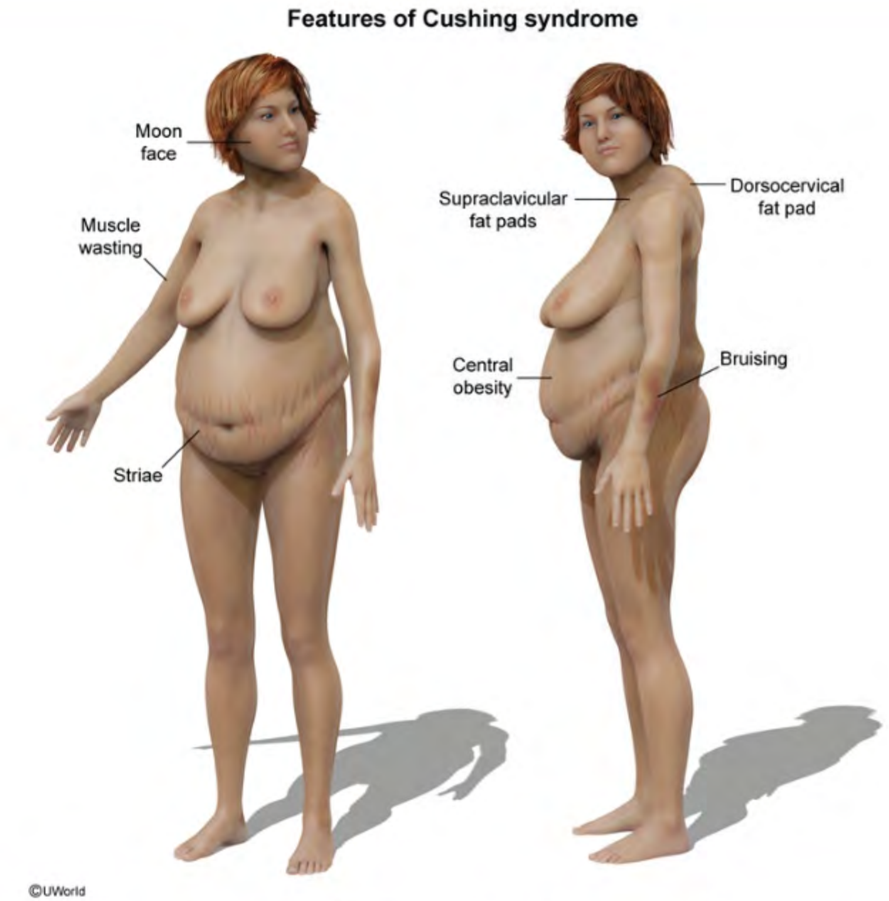
Educational objective:
High levels of cortisol, as seen in patients with Cushing syndrome, frequently cause hypertension due to the increased production of angiotensinogen, adrenergic hypersensitivity, and activation of renal mineralocorticoid receptors, which induces sodium reabsorption. The combined effect leads to expanded blood volume and increased systemic vascular resistance.

References

- The pathophysiology and treatment of hypertension in patients with Cushing's syndrome

https://t.me/USMLEWorldStep1

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

This p
obesit
cosec
small
be pre

High le
followi

- In
- In
- A

Activa
is ofte
wastin

(Choi
althou
tachyp

(Choi
patien
Given

(Choi
edema

glomerular filtration rate is impaired (eg, elevated creatinine). Also, hyperpigmentation is not seen.

https://t.me/USMLEWorldStep1

A 60-year-old woman comes to the office due to difficulty climbing stairs and dyspnea on exertion over the last 6 weeks. The patient has a 40-pack-year smoking history. Blood pressure is 160/90 mm Hg and pulse is 78/min. Auscultation of the chest reveals decreased breath sounds over the right lung base. Proximal muscle strength is 4 on a scale of 0-5. Skin examination shows scattered ecchymoses. Laboratory results show mild hyperglycemia and elevated 24-hour urinary free cortisol. Serum cortisol level is at the upper limit of normal and is not suppressed following administration of low-dose dexamethasone. Serum ACTH level is elevated. Chest x-ray reveals a right lower lobe lung mass. Which of the following changes are most likely to occur after administration of high-dose dexamethasone in this patient?

	ACTH	Cortisol
○ A.	Decrease	Decrease
○ B.	Increase	Increase
○ C.	Increase	No change
○ D.	No change	Decrease
○ E.	No change	No change

Submit

https://t.me/USMLEWorldStep1

A 60-year-old woman comes to the office due to difficulty climbing stairs and dyspnea on exertion over the last 6 weeks. The patient has a 40-pack-year smoking history. Blood pressure is 160/90 mm Hg and pulse is 78/min. Auscultation of the chest reveals decreased breath sounds over the right lung base. Proximal muscle strength is 4 on a scale of 0-5. Skin examination shows scattered ecchymoses. Laboratory results show mild hyperglycemia and elevated 24-hour urinary free cortisol. Serum cortisol level is at the upper limit of normal and is not suppressed following administration of low-dose dexamethasone. Serum ACTH level is elevated. Chest x-ray reveals a right lower lobe lung mass. Which of the following changes are most likely to occur after administration of high-dose dexamethasone in this patient?

		ACTH	Cortisol	
✗	A.	Decrease	Decrease	(5%)
	B.	Increase	Increase	(2%)
	C.	Increase	No change	(1%)
	D.	No change	Decrease	(8%)
✓	E.	No change	No change	(82%)

Incorrect
Correct answer
E

82%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

Biochemical findings in Cushing syndrome			
Etiology	**ACTH**	**Cortisol**	**High-dose dexamethasone suppression test**
Pituitary adenoma	↑	↑	↓ Cortisol

https://t.me/USMLEWorldStep1

Biochemical findings in Cushing syndrome			
Etiology	**ACTH**	**Cortisol**	**High-dose dexamethasone suppression test**
Pituitary adenoma	↑	↑	↓ Cortisol
Ectopic ACTH secretion	↑	↑	Cortisol remains elevated
Adrenal adenoma/carcinoma	↓	↑	

This patient's hypertension, proximal muscle weakness, and hyperglycemia are suggestive of excess cortisol (ie, **Cushing syndrome** [CS]). Hypercortisolism can be confirmed by finding elevated cortisol levels in a late-night salivary sample or 24-hour urine collection. Additionally, low-dose dexamethasone suppression testing can also be useful for confirming the diagnosis; administration of a small dose of a potent glucocorticoid rapidly suppresses ACTH and cortisol secretion in normal individuals, but patients with CS are resistant to low-dose glucocorticoids so serum cortisol remains elevated.

Once the diagnosis is confirmed, the next step is **establishing the cause** of CS, which involves measurement of serum ACTH levels:

- Low ACTH levels are seen with autonomous adrenal production of cortisol (eg, adrenal adenoma or carcinoma) or exogenous glucocorticoid exposure due to feedback suppression
- **High ACTH** levels occur with pituitary adenomas (ie, Cushing disease) or ectopic ACTH production by nonpituitary tumors, which can be further distinguished with the **high-dose dexamethasone suppression test**:
  - Pituitary sources of ACTH are only relatively resistant to feedback inhibition, and high doses of dexamethasone will suppress ACTH and cortisol levels **(Choice A)**
  - Nonpituitary **ectopic sources** of ACTH (eg, **small cell lung cancer**) are completely resistant to feedback inhibition, and ACTH and cortisol will remain elevated following high doses of dexamethasone

This patient's rapid symptom onset, heavy smoking history, and lung mass are consistent with paraneoplastic CS, likely due to small cell lung cancer. **ACTH and cortisol production** will likely be **unchanged** following high-dose

https://t.me/USMLEWorldStep1

Pituitary adenoma	↑	↑	↓ Cortisol
Ectopic ACTH secretion	↑	↑	Cortisol remains elevated
Adrenal adenoma/carcinoma	↓	↑	

This patient's hypertension, proximal muscle weakness, and hyperglycemia are suggestive of excess cortisol (ie, **Cushing syndrome** [CS]). Hypercortisolism can be confirmed by finding elevated cortisol levels in a late-night salivary sample or 24-hour urine collection. Additionally, low-dose dexamethasone suppression testing can also be useful for confirming the diagnosis; administration of a small dose of a potent glucocorticoid rapidly suppresses ACTH and cortisol secretion in normal individuals, but patients with CS are resistant to low-dose glucocorticoids so serum cortisol remains elevated.

Once the diagnosis is confirmed, the next step is **establishing the cause** of CS, which involves measurement of serum ACTH levels:

- Low ACTH levels are seen with autonomous adrenal production of cortisol (eg, adrenal adenoma or carcinoma) or exogenous glucocorticoid exposure due to feedback suppression
- **High ACTH** levels occur with pituitary adenomas (ie, Cushing disease) or ectopic ACTH production by nonpituitary tumors, which can be further distinguished with the **high-dose dexamethasone suppression test**:
  - Pituitary sources of ACTH are only relatively resistant to feedback inhibition, and high doses of dexamethasone will suppress ACTH and cortisol levels **(Choice A)**
  - Nonpituitary **ectopic sources** of ACTH (eg, **small cell lung cancer**) are completely resistant to feedback inhibition, and ACTH and cortisol will remain elevated following high doses of dexamethasone

This patient's rapid symptom onset, heavy smoking history, and lung mass are consistent with paraneoplastic CS, likely due to small cell lung cancer. **ACTH and cortisol production** will likely be **unchanged** following high-dose dexamethasone.

(Choices B and C) In normal individuals, dexamethasone suppresses ACTH release from the pituitary. In patients with abnormal pituitary or ectopic ACTH production, dexamethasone affects ACTH levels as described

https://t.me/USMLEWorldStep1

serum cortisol remains elevated.

Once the diagnosis is confirmed, the next step is **establishing the cause** of CS, which involves measurement of serum ACTH levels:

- Low ACTH levels are seen with autonomous adrenal production of cortisol (eg, adrenal adenoma or carcinoma) or exogenous glucocorticoid exposure due to feedback suppression
- **High ACTH** levels occur with pituitary adenomas (ie, Cushing disease) or ectopic ACTH production by nonpituitary tumors, which can be further distinguished with the **high-dose dexamethasone suppression test**:
  - Pituitary sources of ACTH are only relatively resistant to feedback inhibition, and high doses of dexamethasone will suppress ACTH and cortisol levels **(Choice A)**
  - Nonpituitary **ectopic sources** of ACTH (eg, **small cell lung cancer**) are completely resistant to feedback inhibition, and ACTH and cortisol will remain elevated following high doses of dexamethasone

This patient's rapid symptom onset, heavy smoking history, and lung mass are consistent with paraneoplastic CS, likely due to small cell lung cancer. **ACTH and cortisol production** will likely be **unchanged** following high-dose dexamethasone.

(Choices B and C) In normal individuals, dexamethasone suppresses ACTH release from the pituitary. In patients with abnormal pituitary or ectopic ACTH production, dexamethasone affects ACTH levels as described above. However, dexamethasone does not stimulate ACTH release in any setting.

(Choice D) The fall in cortisol seen in dexamethasone suppression tests is due to feedback suppression causing decreased ACTH release. A fall in cortisol would not be seen without a corresponding fall in ACTH.

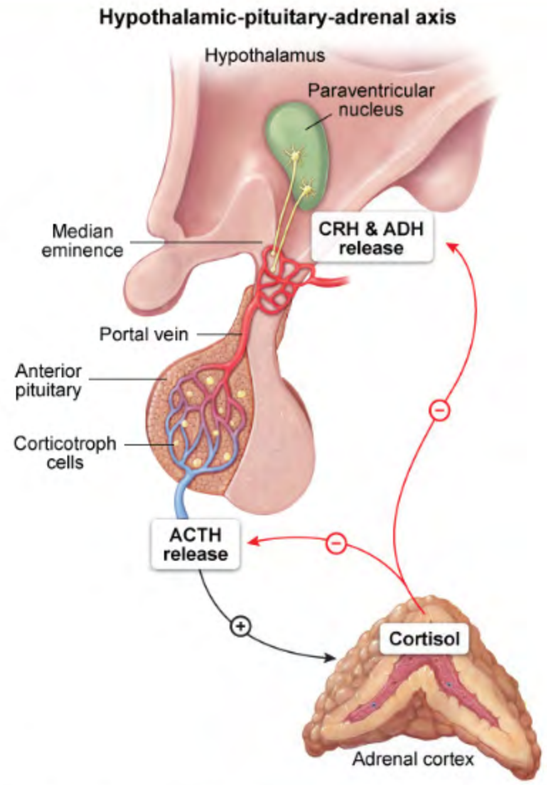
Educational objective:
Cushing syndrome caused by a pituitary adenoma or ectopic (paraneoplastic) ACTH secretion is associated with elevated ACTH levels. High-dose dexamethasone suppresses ACTH and cortisol secretion when Cushing syndrome is caused by a pituitary adenoma (Cushing disease) but not when it is caused by ectopic ACTH secretion (eg, small cell lung cancer).

References

https://t.me/USMLEWorldStep1

Pituitary adenoma	↑	↑	↓ Cortisol

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

This p
Cushi
salivar
useful
ACTH
serum

Once
serum

- L
  c
- **H**
  n
  te

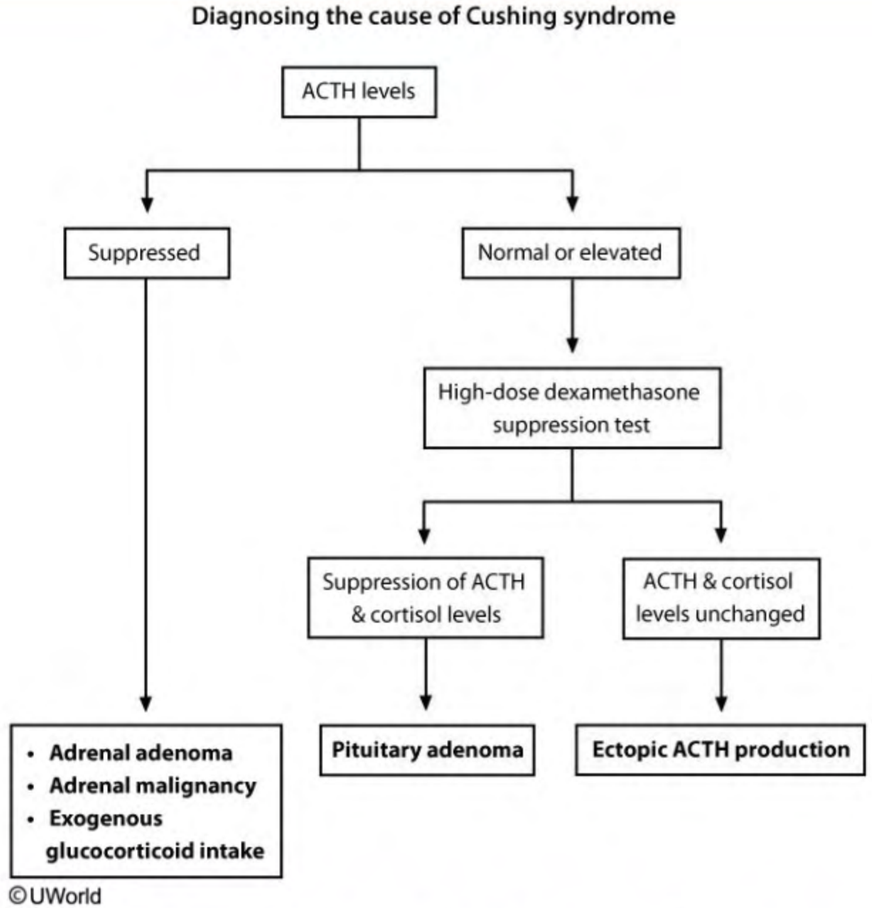
This p
likely due to small cell lung cancer. **ACTH and cortisol production** will likely be **unchanged** following high dose dexamethasone.

(Choices B and C) In normal individuals, dexamethasone suppresses ACTH release from the pituitary. In patients with abnormal pituitary or ectopic ACTH production, dexamethasone affects ACTH levels as described

https://t.me/USMLEWorldStep1

Pituitary adenoma	↑	↑	↓ Cortisol

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

This p
Cushi
salivar
useful
ACTH
serum

Once
serum

- L
  c
- **H**
  n
  te

This p
likely
dexam

(Choices B and C) In normal individuals, dexamethasone suppresses ACTH release from the pituitary. In

https://t.me/USMLEWorldStep1

An 18-month-old child is brought to the office for evaluation of delayed walking and lower limb deformity. The mother has short stature and underwent corrective surgery for bowed legs when she was an adolescent. Vital signs are within normal limits. Examination shows delayed developmental milestones for gross motor function but age-appropriate findings for social function, vision, speech, and hearing. Musculoskeletal examination reveals widening of the knee joints with significant bowing of the legs. Serum laboratory results are as follows:

Calcium	normal
Phosphorus	low
25-hydroxyvitamin D	normal
1,25-dihydroxyvitamin D	normal
Parathyroid hormone	normal

Which of the following is the most likely cause of this patient's current condition?

- A. Decreased dietary calcium intake
- B. Deficiency of 1-alpha-hydroxylase
- C. Hereditary resistance to vitamin D
- D. Increased urinary phosphate excretion

Submit

https://t.me/USMLEWorldStep1

An 18-month-old child is brought to the office for evaluation of delayed walking and lower limb deformity. The mother has short stature and underwent corrective surgery for bowed legs when she was an adolescent. Vital signs are within normal limits. Examination shows delayed developmental milestones for gross motor function but age-appropriate findings for social function, vision, speech, and hearing. Musculoskeletal examination reveals widening of the knee joints with significant bowing of the legs. Serum laboratory results are as follows:

Calcium	normal
Phosphorus	low
25-hydroxyvitamin D	normal
1,25-dihydroxyvitamin D	normal
Parathyroid hormone	normal

Which of the following is the most likely cause of this patient's current condition?

- ✗ A. Decreased dietary calcium intake (2%)
- B. Deficiency of 1-alpha-hydroxylase (7%)
- C. Hereditary resistance to vitamin D (42%)
- ✓ D. Increased urinary phosphate excretion (47%)

Incorrect
Correct answer
D

47%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

Evaluation of rickets

Clinical manifestations

https://t.me/USMLEWorldStep1

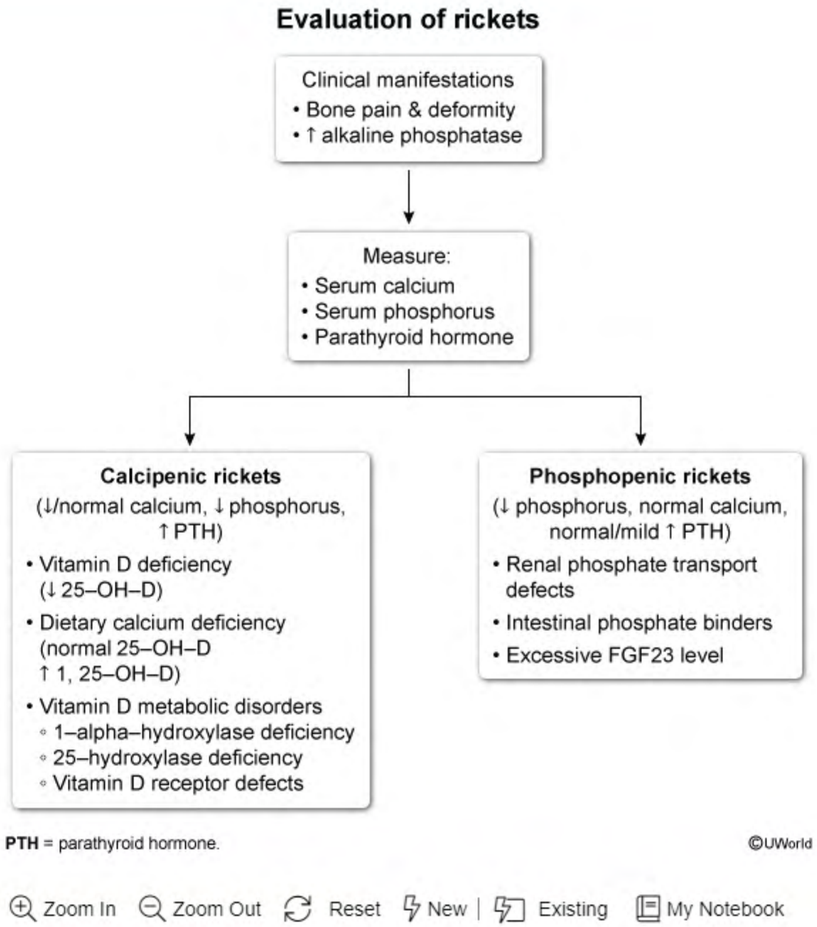
An 18-month-old child is brought to the office for evaluation of delayed walking and lower limb deformity. The mothe
signs
age-ap
widen

Which

Inco
Corre
D

Expl

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Clinical manifestations

https://t.me/USMLEWorldStep1

This patient with lower extremity bowing and enlarged knee epiphyses has rickets. Clinical manifestations reflect defective mineralization at sites of rapid bone growth, leading to thickening and disorganization of growth plate cartilage and accumulation of unmineralized osteoid in the adjacent metaphysis.

Rickets can be **categorized as calcipenic** (low calcium) **or phosphopenic** (low phosphorus). Calcipenic rickets can be due to low calcium intake or to deficiency or metabolic disorders (eg, receptor defects) of vitamin D, which cause reduced intestinal calcium absorption. This patient has a normal serum calcium level with no compensatory rise in parathyroid hormone (PTH), suggesting **adequate calcium intake**. The patient's 25-hydroxy- and 1,25-dihydroxyvitamin D levels also are normal, suggesting **normal vitamin D** stores and metabolism; if there were vitamin D resistance (receptor defect), the vitamin D levels would likely be higher and serum calcium would be low.

This patient's only abnormality is low serum phosphorus, consistent with **phosphopenic rickets**. The most common cause is a primary defect in **renal phosphate reabsorption** (eg, hereditary hypophosphatemic rickets).

(Choice A) Rickets due to dietary calcium deficiency (not increased intake) causes a compensatory rise in PTH, which can restore serum calcium levels to normal or near normal. Since PTH upregulates 1-alpha-hydroxylase, patients will also have an elevated 1,25-dihydroxyvitamin D level.

(Choice B) 1-alpha-hydroxylase converts 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D (the more active form). Deficiency can cause rickets (ie, vitamin D–dependent rickets type 1), but 1,25-dihydroxyvitamin D levels would be low.

(Choice C) Hereditary vitamin D–resistant rickets is caused by vitamin D receptor mutations. The loss of vitamin D effect causes decreased intestinal calcium absorption, lowering serum calcium; the compensatory rise in PTH induces 1-alpha-hydroxylase activity, raising 1,25-dihydroxyvitamin D levels above normal values (unlike this patient).

Educational objective:
Rickets is characterized by defective mineralization at sites of rapid bone growth. It can be due to deficiency of calcium or phosphorus. Calcium deficiency conditions are mainly due to vitamin D abnormalities or low dietary calcium intake. Phosphorus deficiency is usually due to impaired renal reabsorption.

References

https://t.me/USMLEWorldStep1

This patient with lower extremity bowing and enlarged knee epiphyses has rickets. Clinical manifestations reflect defect cartila

Ricket can be cause rise in dihydr vitami

This p comm

(Choi which patien

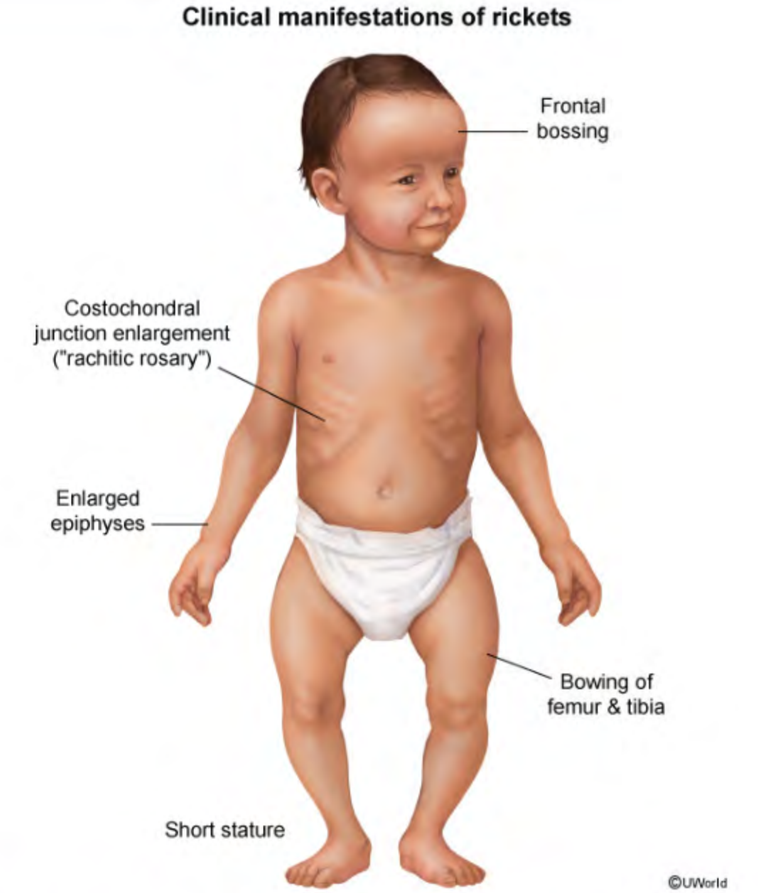
(Choi Deficie low.

(Choi D effe induce patien

Educa Ricket calciu calciu

References

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

A 66-year-old man comes to the office due to progressive vision impairment over the last year that has begun to affect his ability to drive. He has difficulty reading road signs at night and reports excessive glare from the headlights of oncoming cars. The patient has a long history of hypertension and type 2 diabetes mellitus. Funduscopy reveals a diminished red reflex bilaterally with obscuration of retinal detail. It is determined that the patient's condition is in part due to intracellular accumulation of sorbitol. In healthy cells, this sugar alcohol is normally metabolized into which of the following substances to facilitate excretion?

- A. Fructose
- B. Galactitol
- C. Galactose
- D. Glucose
- E. Xylulose

Submit

https://t.me/USMLEWorldStep1

A 66-year-old man comes to the office due to progressive vision impairment over the last year that has begun to affect his ability to drive. He has difficulty reading road signs at night and reports excessive glare from the headlights of oncoming cars. The patient has a long history of hypertension and type 2 diabetes mellitus. Funduscopy reveals a diminished red reflex bilaterally with obscuration of retinal detail. It is determined that the patient's condition is in part due to intracellular accumulation of sorbitol. In healthy cells, this sugar alcohol is normally metabolized into which of the following substances to facilitate excretion?

- ✓ A. Fructose (62%)
- B. Galactitol (16%)
- C. Galactose (6%)
- D. Glucose (8%)
- E. Xylulose (6%)

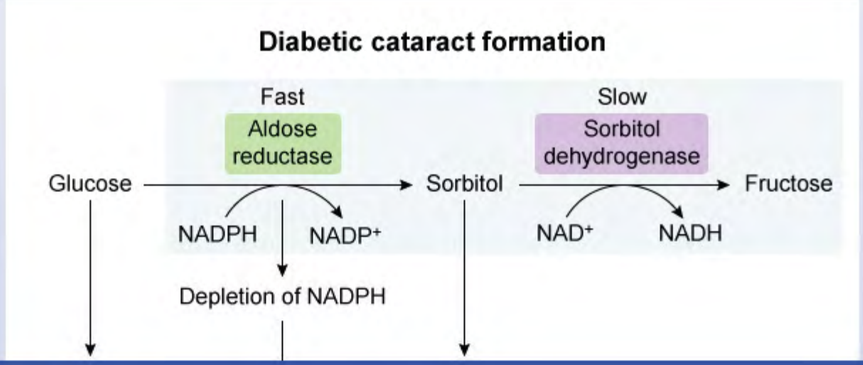
Correct

62% Answered correctly

03 secs Time Spent

2023 Version

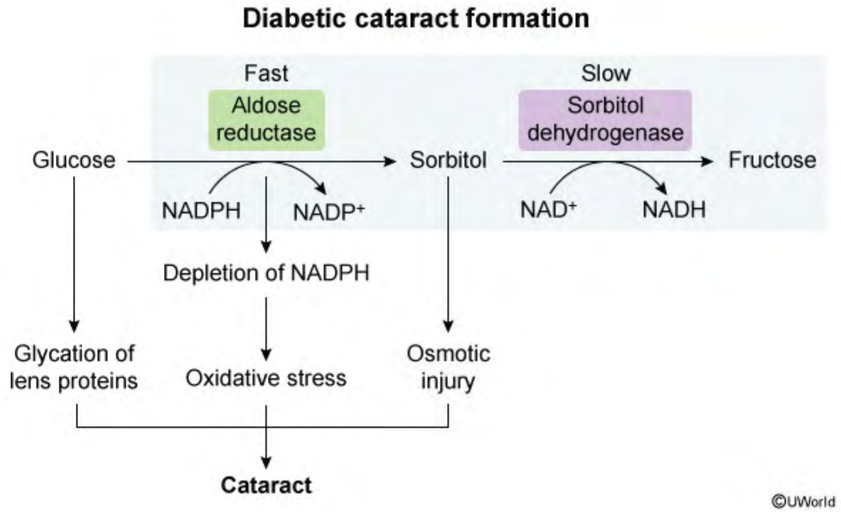
Explanation



https://t.me/USMLEWorldStep1

C. Galactose (6%)

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

This p
decrea
age; o
In this
the polyol pathway.

https://t.me/USMLEWorldStep1

This patient has **cataracts**, a vision-impairing opacification of the lens that causes loss of the red reflex with decreased visualization of retinal details on ophthalmoscopic evaluation. The incidence of cataracts increases with **age**; other risk factors include smoking, excessive sunlight exposure, **diabetes mellitus**, and glucocorticoid use. In this patient, long-term hyperglycemia most likely contributed to cataract formation by causing **oversaturation of the polyol pathway**.

The first step in the polyol pathway (an alternative route of glucose metabolism) is the conversion of glucose into sorbitol by aldose reductase. Sorbitol cannot readily cross cell membranes and is therefore trapped inside the cells where it forms. The second enzyme in the pathway, sorbitol dehydrogenase, is able to **convert sorbitol into fructose** at a sufficient rate to prevent accumulation when glucose levels are normal. However, the process is slow; in long-standing hyperglycemia, sorbitol accumulates in tissues with lower sorbitol dehydrogenase activity, such as the retina, lens, kidney, and peripheral nerves.

Sorbitol accumulation increases cellular **osmotic and oxidative stress** and contributes to the pathogenesis of diabetic retinopathy, neuropathy, and nephropathy. In lens cells, the increased stress leads to the development of hydropic lens fibers that degenerate, eventually resulting in lens opacification and cataract formation.

(Choices B and C) Another function of aldose reductase is the conversion of galactose into galactitol (ie, this enzyme converts sugars into their corresponding sugar alcohols). Galactitol production via this pathway is normally insignificant. In galactosemia (galactose-1-phosphate uridyltransferase deficiency), an increased amount of galactitol is produced, resulting in congenital cataracts.

(Choice D) The end product of sorbitol metabolism in most cells is fructose (not glucose), which is then excreted by the cells and taken up by the liver to produce glucose and triglycerides.

(Choice E) Xylulose is an intermediate in the pentose phosphate pathway, which is used to generate NADPH (for cholesterol and fatty acid synthesis) and ribose 5-phosphate (for nucleotide synthesis).

Educational objective:
In the polyol pathway, aldose reductase converts glucose into sorbitol, which is slowly metabolized into fructose by sorbitol dehydrogenase. Chronic hyperglycemia overwhelms this pathway, causing intracellular sorbitol accumulation and increased osmotic/oxidative stress. This accelerates cataract development in patients with

https://t.me/USMLEWorldStep1

In this patient, long-term hyperglycemia most likely contributed to cataract formation by causing **oversaturation of the polyol pathway**.

The first step in the polyol pathway (an alternative route of glucose metabolism) is the conversion of glucose into sorbitol by aldose reductase. Sorbitol cannot readily cross cell membranes and is therefore trapped inside the cells where it forms. The second enzyme in the pathway, sorbitol dehydrogenase, is able to **convert sorbitol into fructose** at a sufficient rate to prevent accumulation when glucose levels are normal. However, the process is slow; in long-standing hyperglycemia, sorbitol accumulates in tissues with lower sorbitol dehydrogenase activity, such as the retina, lens, kidney, and peripheral nerves.

Sorbitol accumulation increases cellular **osmotic and oxidative stress** and contributes to the pathogenesis of diabetic retinopathy, neuropathy, and nephropathy. In lens cells, the increased stress leads to the development of hydropic lens fibers that degenerate, eventually resulting in lens opacification and cataract formation.

(Choices B and C) Another function of aldose reductase is the conversion of galactose into galactitol (ie, this enzyme converts sugars into their corresponding sugar alcohols). Galactitol production via this pathway is normally insignificant. In galactosemia (galactose-1-phosphate uridyltransferase deficiency), an increased amount of galactitol is produced, resulting in congenital cataracts.

(Choice D) The end product of sorbitol metabolism in most cells is fructose (not glucose), which is then excreted by the cells and taken up by the liver to produce glucose and triglycerides.

(Choice E) Xylulose is an intermediate in the pentose phosphate pathway, which is used to generate NADPH (for cholesterol and fatty acid synthesis) and ribose 5-phosphate (for nucleotide synthesis).

Educational objective:
In the polyol pathway, aldose reductase converts glucose into sorbitol, which is slowly metabolized into fructose by sorbitol dehydrogenase. Chronic hyperglycemia overwhelms this pathway, causing intracellular sorbitol accumulation and increased osmotic/oxidative stress. This accelerates cataract development in patients with diabetes, and contributes to the pathogenesis of diabetic retinopathy, neuropathy, and nephropathy.

References

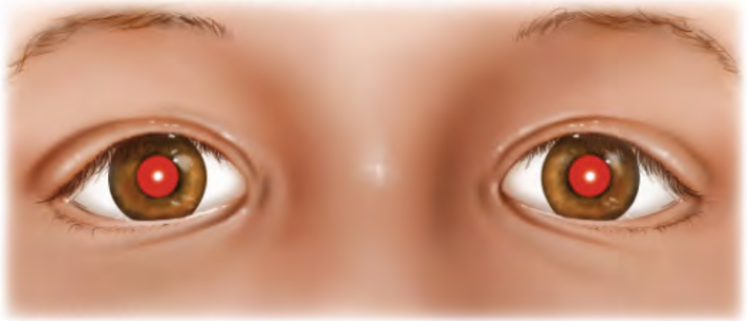
- The sorbitol pathway in the human lens: aldose reductase and polyol dehydrogenase.

https://t.me/USMLEWorldStep1

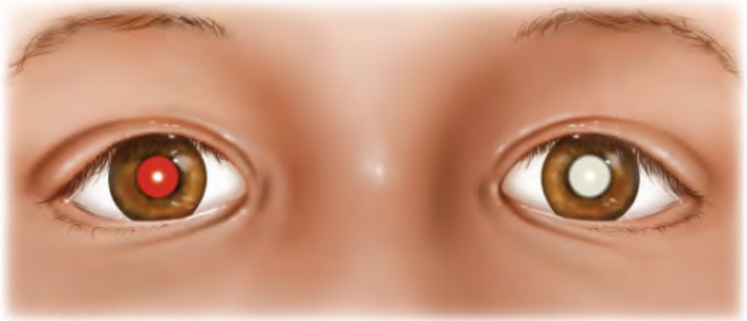
Depletion of NADPH

Exhibit Display

Normal eyes & white reflex



Normal eyes
Red reflexes & corneal light reflexes are equal.



Absent reflex
White reflex on abnormal eye can result from opacities of the lens (eg, cataract) or tumor (eg, retinoblastoma).

©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

This p
decrea
age; o
In this
the po

The fir
sorbito
cells w
fructo
slow; i
such a

Sorbit
diabet
hydrop

(Choi
enzym
norma
of gala

(Choi
by the cells and taken up by the liver to produce glucose and triglycerides.

https://t.me/USMLEWorldStep1

A 6-year-old girl is brought to the office by her mother due to pubertal development over the past year. The mother has noticed that her daughter has developed breasts and is also much taller than most of her classmates. Weight is at the 50th percentile and height is at the 95th percentile. Physical examination reveals Tanner stage 3 breast development and coarse pubic hair. She is diagnosed with idiopathic precocious puberty. Without treatment, this patient's projected height will most likely be shorter than average due to which of the following hormonal effects?

- A. Estrogen effect on the long bone diaphysis
- B. Estrogen effect on the long bone epiphysis
- C. Estrogen effect on the long bone epiphyseal plate
- D. Insulin-like growth factor 1 effect on the long bone diaphysis
- E. Insulin-like growth factor 1 effect on the long bone epiphyseal plate

Submit

https://t.me/USMLEWorldStep1

A 6-year-old girl is brought to the office by her mother due to pubertal development over the past year. The mother has noticed that her daughter has developed breasts and is also much taller than most of her classmates. Weight is at the 50th percentile and height is at the 95th percentile. Physical examination reveals Tanner stage 3 breast development and coarse pubic hair. She is diagnosed with idiopathic precocious puberty. Without treatment, this patient's projected height will most likely be shorter than average due to which of the following hormonal effects?

- A. Estrogen effect on the long bone diaphysis (14%)
- ✕ B. Estrogen effect on the long bone epiphysis (54%)
- ✓ C. Estrogen effect on the long bone epiphyseal plate (17%)
- D. Insulin-like growth factor 1 effect on the long bone diaphysis (9%)
- E. Insulin-like growth factor 1 effect on the long bone epiphyseal plate (4%)

Incorrect
Correct answer
C

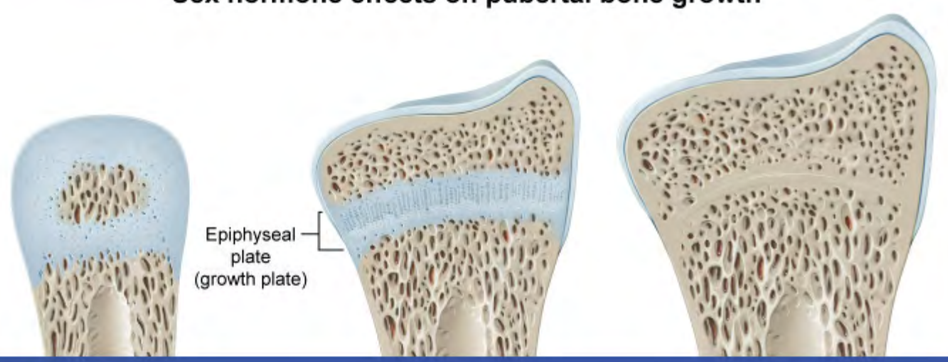
17%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

Sex hormone effects on pubertal bone growth



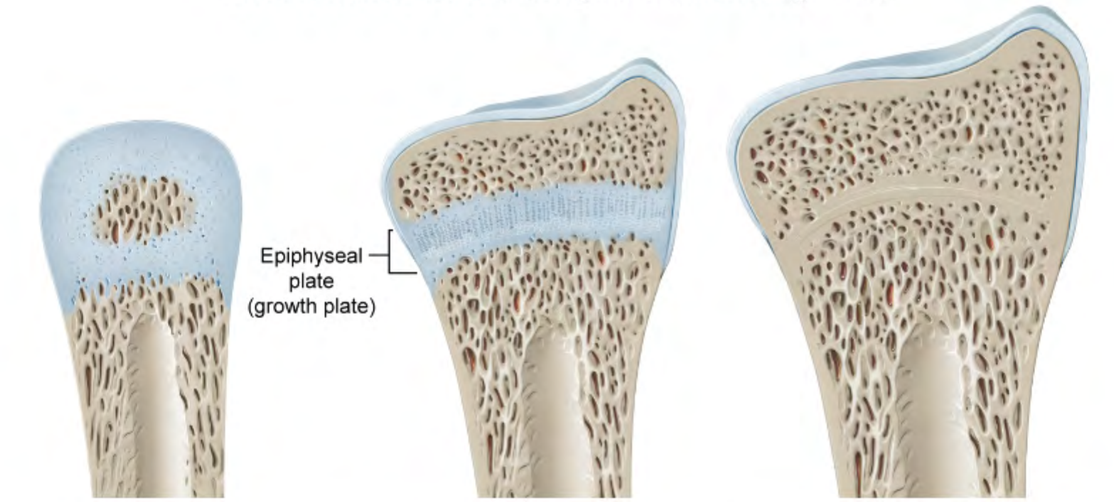
https://t.me/USMLEWorldStep1

Incorrect
Correct answer
C

17%
03 secs
2023

Exhibit Display

Sex hormone effects on pubertal bone growth



Prepuberty	Puberty	Late puberty
Low estrogen/testosterone	↑ Estrogen/testosterone & GH/IGF-1 ↓ Rapid linear growth (growth spurt)	↑↑ Estrogen (estradiol) ↓ Proliferative exhaustion of chondrocytes ↓ Growth plate closure

GH = growth hormone; **IGF** = insulin-like growth factor.

©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Norma
pulsati
triggers ovarian estrogen production. Precocious puberty, defined in girls as the development of secondary sexual
characteristics at age <8, is often caused by early maturation of this hormonal axis, or **idiopathic precocious**

https://t.me/USMLEWorldStep1

GH = growth hormone; IGF = insulin-like growth factor.

©UWorld

Normal pubertal development in girls manifests with secondary sexual characteristics at age ≥8 and is due to pulsatile GnRH secretion from the hypothalamus. This stimulates LH and FSH release from the pituitary, which triggers ovarian estrogen production. Precocious puberty, defined in girls as the development of secondary sexual characteristics at age <8, is often caused by early maturation of this hormonal axis, or **idiopathic precocious puberty**. This condition is gonadotropin-dependent and characterized by early-onset **pulsatile GnRH** secretion, resulting in rising **estrogen production** in young girls.

Major actions of estrogen include stimulation of **breast development** and bone growth. A growth spurt occurs during early puberty primarily due to positive feedback by estrogen on growth hormone (GH) production. GH stimulates insulin-like growth factor 1 (IGF-1) synthesis, which leads to the differentiation and proliferation of chondrocytes in the epiphyseal plate and therefore increased linear growth **(Choices D and E)**. This rapid growth explains this patient's height at the 95th percentile, and the growth spurt typically results in achievement of 90% of final adult height.

At high doses, estradiol, a potent estrogen-derived steroid hormone, promotes senescence of chondrocytes and therefore **closure of the epiphyseal plate** (ie, growth plate) **(Choices A and B)**. Once it is closed, linear growth is irreversibly stopped. Although this patient is now taller than her peers, **without treatment**, excess estrogens will cause the growth plates to close prematurely, and she will be **shorter** than average. Treatment of central precocious puberty is typically with a GnRH agonist, which causes continuous (rather than pulsatile) stimulation of the gonadotrophs, leading to decreased sex hormone production.

Educational objective:
Idiopathic precocious puberty is characterized by early-onset, pulsatile GnRH secretion, resulting in increased estrogen production. Estrogens promote bone growth but also epiphyseal plate (ie, growth plate) closure, so without treatment, patients typically have an early growth spurt but a shorter-than-expected adult height.

References

- Gonadotropin releasing hormone agonist treatment to increase final stature in children with precocious puberty: a meta-analysis.

https://t.me/USMLEWorldStep1

GH = growth hormone; IGF = insulin-like growth factor.

©UWorld

Norma
pulsati
trigger
charac
puber
resulti

Major
during
stimul
chond
explai
final a

At high
therefo
irrever
cause
precoc
the go

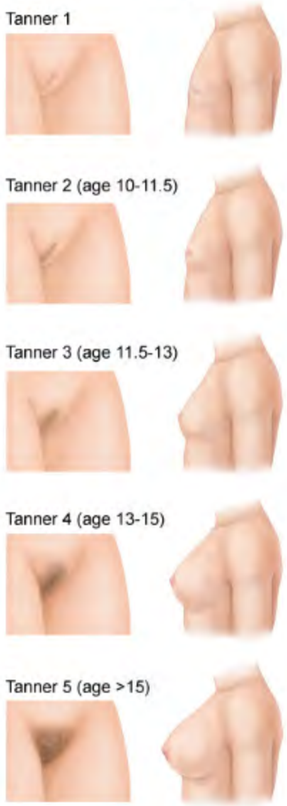
Educa
Idiopa
estrog
withou

Refere

- Go
  a meta-analysis.

Exhibit Display

Tanner stages



Note: ages represent mean ages of development.

©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

GH = growth hormone; IGF = insulin-like growth factor.

©UWorld

Norma
pulsati
trigger
charac
puber
resulti

Major
during
stimul
chond
explai
final a

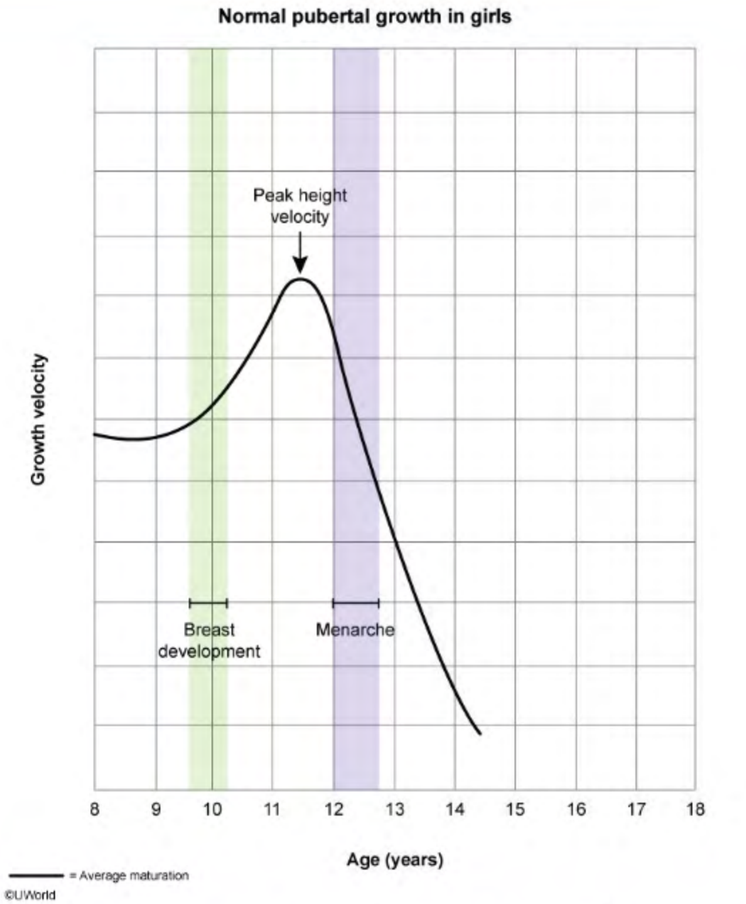
At high
therefo
irrever
cause
precoc
the go

Educa
Idiopa
estrog
withou

Refere

- Go
  a meta-analysis.

Exhibit Display



Zoom In Zoom Out Reset New | Existing My Notebook

https://t.me/USMLEWorldStep1

GH = growth hormone; IGF = insulin-like growth factor.

©UWorld

Norma
pulsati
trigger
charac
puber
resulti

Major
during
stimul
chond
explai
final a

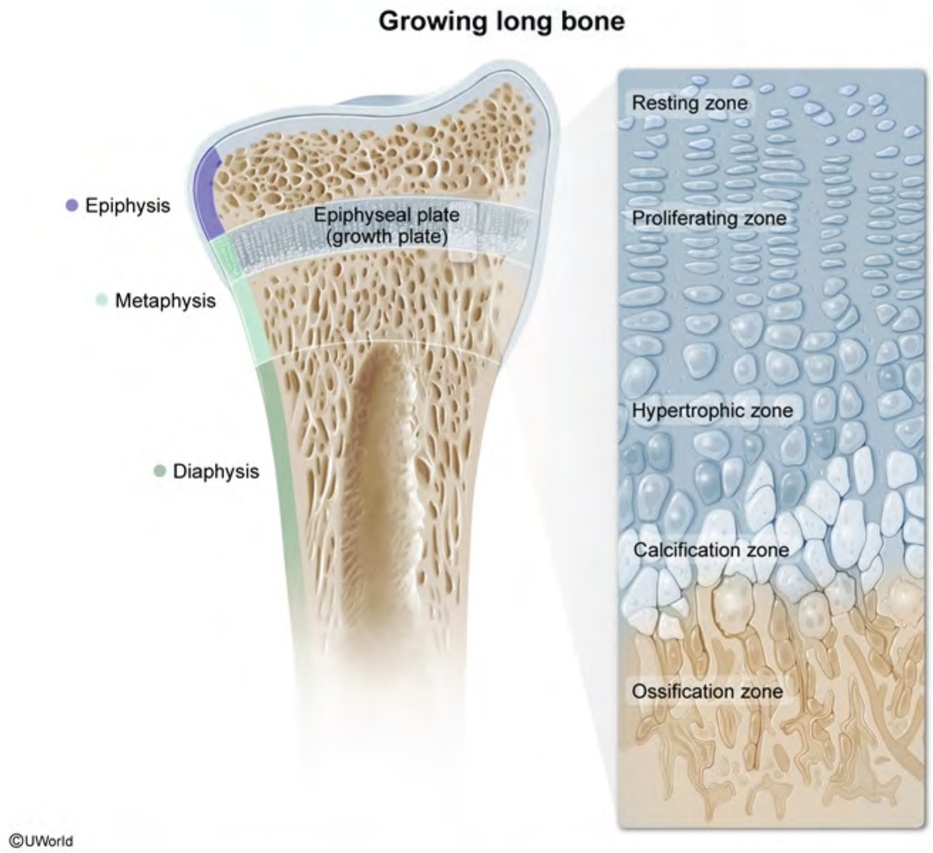
At high
therefo
irrever
cause
precoc
the go

Educa
Idiopa
estrog
withou

Refere

- Go
  a meta-analysis.

Exhibit Display



Zoom In Zoom Out Reset New | Existing My Notebook

https://t.me/USMLEWorldStep1

A 45-year-old woman is evaluated 2 weeks after she fractured her left radius during a fall from standing height. Two months previously, she passed a renal stone. There is no family history of osteoporosis or hypercalcemia. Physical examination is unremarkable. Serum laboratory results are as follows:

Calcium	11.3 mg/dL
Phosphorus	2.4 mg/dL
Creatinine	1.0 mg/dL
Albumin	4.1 g/dL
Parathyroid hormone	75 pg/mL (normal: 10-65)

Bone density testing performed using dual-energy x-ray absorptiometry reveals osteoporosis. Which of the following is the major contributor to bone loss in this patient?

- A. Decreased bone formation due to decreased conversion of calcidiol to calcitriol
- B. Decreased bone formation due to excessive loss of calcium in urine
- C. Decreased bone formation due to inhibition of osteoblast differentiation
- D. Increased bone resorption due to decreased intestinal calcium absorption
- E. Increased bone resorption due to paracrine stimulation of osteoclasts

Submit

https://t.me/USMLEWorldStep1

A 45-year-old woman is evaluated 2 weeks after she fractured her left radius during a fall from standing height. Two months previously, she passed a renal stone. There is no family history of osteoporosis or hypercalcemia. Physical examination is unremarkable. Serum laboratory results are as follows:

Calcium	11.3 mg/dL
Phosphorus	2.4 mg/dL
Creatinine	1.0 mg/dL
Albumin	4.1 g/dL
Parathyroid hormone	75 pg/mL (normal: 10-65)

Bone density testing performed using dual-energy x-ray absorptiometry reveals osteoporosis. Which of the following is the major contributor to bone loss in this patient?

- A. Decreased bone formation due to decreased conversion of calcidiol to calcitriol (2%)
- ✗ B. Decreased bone formation due to excessive loss of calcium in urine (5%)
- C. Decreased bone formation due to inhibition of osteoblast differentiation (7%)
- D. Increased bone resorption due to decreased intestinal calcium absorption (6%)
- ✓ E. Increased bone resorption due to paracrine stimulation of osteoclasts (78%)

Incorrect
Correct answer
E

78%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

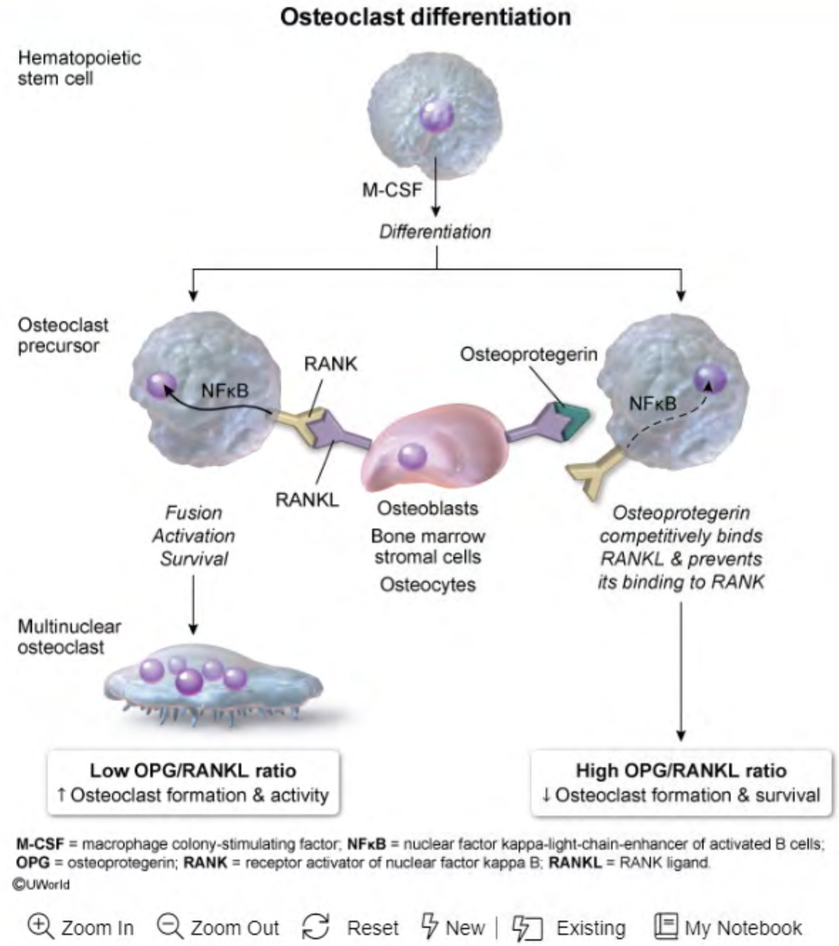
Osteoclast differentiation

Hematopoietic

https://t.me/USMLEWorldStep1

Explanation

Exhibit Display



Zoom In Zoom Out Reset New | Existing My Notebook

This patient has hyperparathyroidism, presenting with **osteoporosis** and nephrolithiasis associated with mild

https://t.me/USMLEWorldStep1

This patient has hyperparathyroidism, presenting with **osteoporosis** and nephrolithiasis associated with mild **hypercalcemia** and an inappropriately **elevated parathyroid hormone** (PTH) level.

PTH increases bone turnover by stimulating the differentiation and activity of osteoblasts, leading to increased bone formation. In addition, PTH upregulates the expression of receptor activator of nuclear factor kappa B ligand (RANK-L) on the surface of the activated osteoblasts, which binds RANK on nearby osteoclast precursor cells and induces maturation to active osteoclasts. Therefore, **PTH** causes **bone formation** (by direct effect on osteoblasts) and **bone resorption** (by paracrine effect on osteoclasts). Bone turnover is normally **balanced**, with bone formation proportionate to resorption.

In **hyperparathyroid states**, continuous exposure to high PTH levels cause increased RANK-L expression along with suppression of osteoprotegerin (a counterregulatory decoy receptor). This leads to greater bone resorption than formation and **net bone loss**.

(Choices A and D) PTH upregulates 1-alpha-hydroxylase in the kidneys, which leads to increased (not decreased) conversion of 25-hydroxyvitamin D (calcidiol) to 1,25-dihydroxyvitamin D (calcitriol). Calcitriol subsequently induces increased (not decreased) intestinal calcium absorption.

(Choice B) PTH increases renal reabsorption of calcium. Despite this, hypercalciuria is common in hyperparathyroidism because the filtered calcium load may exceed renal reabsorption capacity. However, the local concentrations of calcium in the bone remain elevated, and urinary calcium wasting is not a major contributor to bone loss.

(Choice C) Supraphysiologic glucocorticoid (eg, prednisone) doses can cause osteoporosis, in part due to decreased proliferation and differentiation of osteoblast precursor cells. PTH increases the differentiation of osteoblast precursors; osteoporosis occurs in hyperparathyroidism because of a proportionally greater increase in osteoclast activity.

Educational objective:
Parathyroid hormone directly stimulates osteoblasts, leading to increased bone formation. Expression of RANK-L on osteoblasts induces increased bone resorption via a paracrine effect on nearby osteoclasts. Hyperparathyroidism causes increased RANK-L expression and decreased expression of osteoprotegerin, leading

https://t.me/USMLEWorldStep1

PTH increases bone turnover by stimulating the differentiation and activity of osteoblasts, leading to increased bone formation. In addition, PTH upregulates the expression of receptor activator of nuclear factor kappa B ligand (RANK-L) on the surface of the activated osteoblasts, which binds RANK on nearby osteoclast precursor cells and induces maturation to active osteoclasts. Therefore, **PTH** causes **bone formation** (by direct effect on osteoblasts) and **bone resorption** (by paracrine effect on osteoclasts). Bone turnover is normally **balanced**, with bone formation proportionate to resorption.

In **hyperparathyroid states**, continuous exposure to high PTH levels cause increased RANK-L expression along with suppression of osteoprotegerin (a counterregulatory decoy receptor). This leads to greater bone resorption than formation and **net bone loss**.

(Choices A and D) PTH upregulates 1-alpha-hydroxylase in the kidneys, which leads to increased (not decreased) conversion of 25-hydroxyvitamin D (calcidiol) to 1,25-dihydroxyvitamin D (calcitriol). Calcitriol subsequently induces increased (not decreased) intestinal calcium absorption.

(Choice B) PTH increases renal reabsorption of calcium. Despite this, hypercalciuria is common in hyperparathyroidism because the filtered calcium load may exceed renal reabsorption capacity. However, the local concentrations of calcium in the bone remain elevated, and urinary calcium wasting is not a major contributor to bone loss.

(Choice C) Supraphysiologic glucocorticoid (eg, prednisone) doses can cause osteoporosis, in part due to decreased proliferation and differentiation of osteoblast precursor cells. PTH increases the differentiation of osteoblast precursors; osteoporosis occurs in hyperparathyroidism because of a proportionally greater increase in osteoclast activity.

Educational objective:
Parathyroid hormone directly stimulates osteoblasts, leading to increased bone formation. Expression of RANK-L on osteoblasts induces increased bone resorption via a paracrine effect on nearby osteoclasts. Hyperparathyroidism causes increased RANK-L expression and decreased expression of osteoprotegerin, leading to net bone loss.

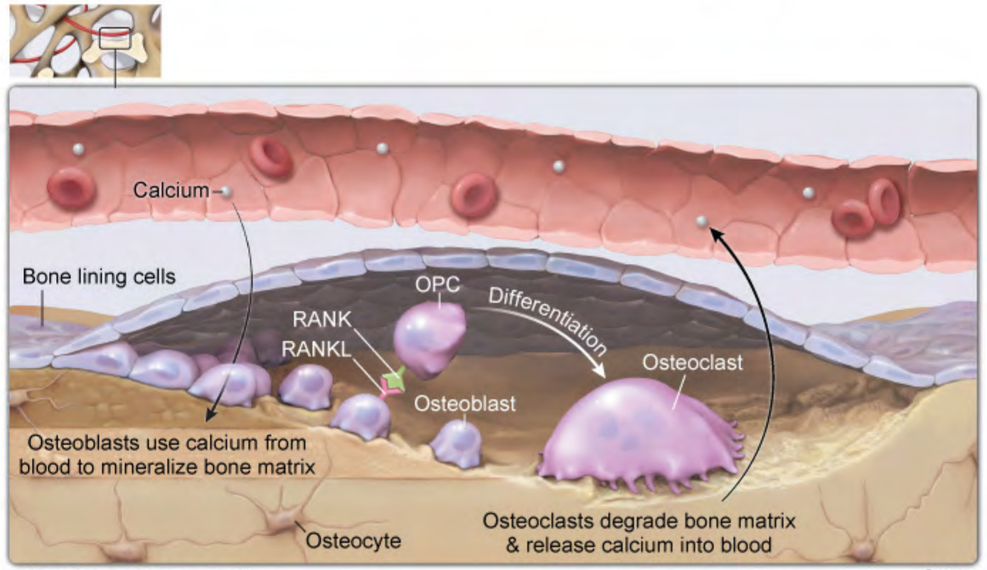
Pathophysiology	Endocrine, Diabetes & Metabolism	Hyperparathyroidism
Subject	System	Topic

https://t.me/USMLEWorldStep1

(growth plate)

Exhibit Display

Regulation of osteoclast progenitor cell differentiation by osteoblasts



OPC = osteoclast precursor cell.

©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Norma
pulsati
trigger
charac
puber
resulti

Major
during
stimula
chond
explai
final a

At high
therefo
irrever

cause the growth plates to close prematurely, and she will be **shorter** than average. Treatment of central

https://t.me/USMLEWorldStep1

A 60-year-old man is brought to the emergency department due to altered mental status. His wife says that he has a nagging cough that seemed to worsen over the past several months and that he also began experiencing occasional dizziness earlier this week. Over the last couple of days, the patient has become increasingly confused, and today he "does not make any sense at all." He has no significant past medical history but has smoked a pack of cigarettes daily for the last 40 years. On physical examination, the patient is incoherent but has an otherwise normal neurologic examination.

Laboratory results are as follows:

Serum chemistry		
	Sodium	120 mEq/L
	Potassium	4.0 mEq/L
	Blood urea nitrogen	12 mg/dL
	Creatinine	0.8 mg/dL
	Calcium	9.0 mg/dL
	Glucose	98 mg/dL
Plasma osmolality		250 mOsm/kg
Urine drug screen		negative

Chest x-ray reveals a mass in the right lung. Which of the following additional findings is most likely to be present in this patient?

- A. Bilateral crackles at the lung bases
- B. Elevated jugular venous pressure
- C. Maximally dilute urine
- D. Normal-appearing volume status

https://t.me/USMLEWorldStep1

confused, and today he "does not make any sense at all." He has no significant past medical history but has smoked a pack of cigarettes daily for the last 40 years. On physical examination, the patient is incoherent but has an otherwise normal neurologic examination.

Laboratory results are as follows:

Serum chemistry	
Sodium	120 mEq/L
Potassium	4.0 mEq/L
Blood urea nitrogen	12 mg/dL
Creatinine	0.8 mg/dL
Calcium	9.0 mg/dL
Glucose	98 mg/dL
Plasma osmolality	250 mOsm/kg
Urine drug screen	negative

Chest x-ray reveals a mass in the right lung. Which of the following additional findings is most likely to be present in this patient?

- A. Bilateral crackles at the lung bases
- B. Elevated jugular venous pressure
- C. Maximally dilute urine
- D. Normal-appearing volume status
- E. Peripheral edema

Submit

https://t.me/USMLEWorldStep1

smoked a pack of cigarettes daily for the last 40 years. On physical examination, the patient is incoherent but has an otherwise normal neurologic examination.

Laboratory results are as follows:

Serum chemistry	
Sodium	120 mEq/L
Potassium	4.0 mEq/L
Blood urea nitrogen	12 mg/dL
Creatinine	0.8 mg/dL
Calcium	9.0 mg/dL
Glucose	98 mg/dL
Plasma osmolality	250 mOsm/kg
Urine drug screen	negative

Chest x-ray reveals a mass in the right lung. Which of the following additional findings is most likely to be present in this patient?

- ✗ A. Bilateral crackles at the lung bases (5%)
- B. Elevated jugular venous pressure (11%)
- C. Maximally dilute urine (18%)
- ✓ D. Normal-appearing volume status (39%)
- E. Peripheral edema (24%)

Incorrect
Correct answer
D

39%
Answered correctly

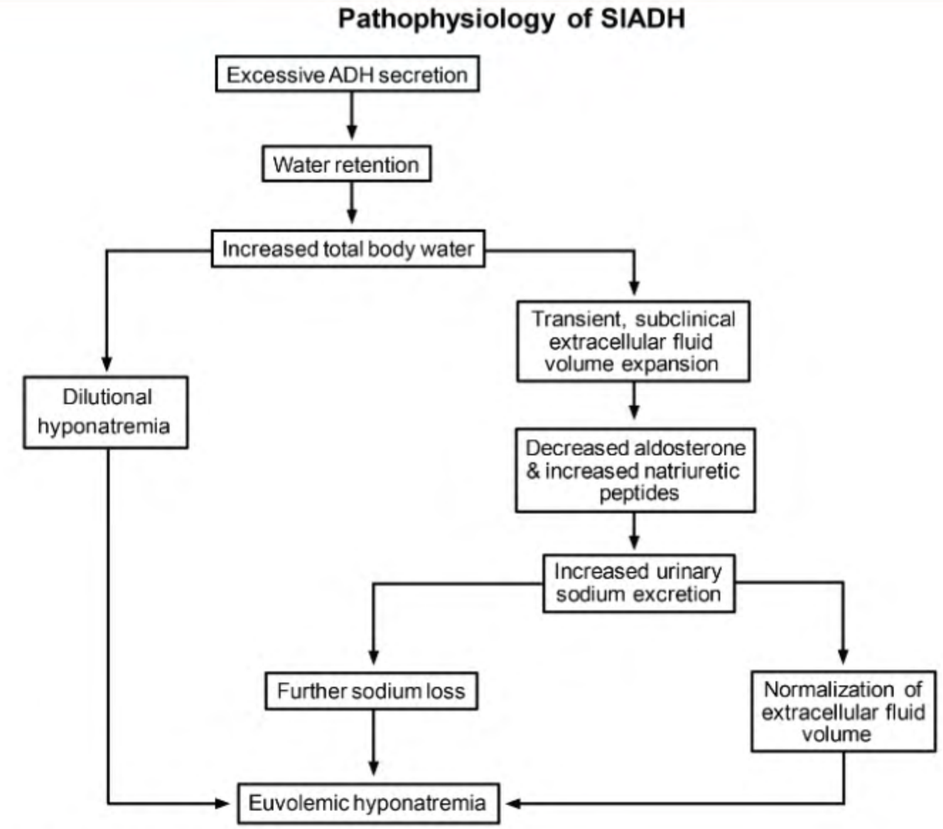
06 secs
Time Spent

2023
Version

https://t.me/USMLEWorldStep1

Explanation

Exhibit Display



SIADH = syndrome of inappropriate antidiuretic hormone.

©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

This p
antidiu
and se
However, **small cell lung carcinomas**, which are tumors of neuroendocrine origin, often release ADH independent of feedback inhibition (paraneoplastic effect). This inappropriate secretion of ADH leads to hyponatremia,

https://t.me/USMLEWorldStep1



SIADH = syndrome of inappropriate antidiuretic hormone.

©UWorld

This patient's combination of hyponatremia and a lung mass is suggestive of the syndrome of inappropriate antidiuretic hormone secretion (**SIADH**). Antidiuretic hormone (ADH) is normally produced in the hypothalamus and secreted from the posterior pituitary in response to changes in plasma osmolality and intravascular volume. However, **small cell lung carcinomas**, which are tumors of neuroendocrine origin, often release ADH independent of feedback inhibition (paraneoplastic effect). This inappropriate secretion of ADH leads to hyponatremia, decreased plasma osmolality, and elevated urine osmolality (which normally should be <100 mOsm/kg when hyponatremia is present). The profound hyponatremia that occurs in SIADH can cause headache, weakness, **altered mental status**, and seizures.

In SIADH, increased ADH causes excessive water absorption by the kidneys, leading to a transient, subclinical hypervolemia. This mild increase in extracellular fluid volume suppresses the renin-aldosterone axis and stimulates the production of natriuretic peptides, leading to excretion of sodium in the urine (natriuresis). As a result, patients with SIADH have a **clinically normal extracellular fluid volume** and low plasma osmolality (**euvolemic hyponatremia**). Features of volume overload (eg, peripheral edema, pulmonary crackles, elevated jugular venous pressure) are not seen **(Choices A, B, and E)**.

(Choice C) Patients with SIADH have inappropriately concentrated urine (generally >100 mOsm/kg) for their degree of hyponatremia. Hyponatremia with a urine osmolality of <100 mOsm/kg (maximally dilute urine) indicates appropriate suppression of ADH secretion (as would be seen in primary polydipsia).

Educational objective:
The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is characterized by low plasma sodium and osmolality, inappropriately concentrated urine, and clinically normal volume status (euvolemic hyponatremia). An important cause of SIADH is a paraneoplastic effect secondary to small cell carcinoma of the lung.

Pathophysiology	Endocrine, Diabetes & Metabolism	SIADH
Subject	System	Topic

Copyright © UWorld. All rights reserved.

https://t.me/USMLEWorldStep1

SIADH = syndrome of inappropriate antidiuretic hormone.

Exhibit Display

Common causes of the syndrome of inappropriate antidiuretic hormone secretion
• CNS disruptions (eg, stroke, infection, trauma, neurosurgery) • Malignancies (eg, small cell lung carcinoma) • Drugs (eg, desmopressin, chlorpropamide, carbamazepine) • Pulmonary disorders (eg, pneumonia, tuberculosis, ventilator use)

New | Existing My Notebook

This p
antidiu
and se
Howev
of feed
decrea
hypon
altere

In SIA
hyperv
stimula
result,
(**euvol**
jugular

(Choi
degree
approp

Educa
The sy
osmol
import

Pathoph
Subject

Copyright © UWorld. All rights reserved.

https://t.me/USMLEWorldStep1

SIADH = syndrome of inappropriate antidiuretic hormone.

Exhibit Display

This p
antidiu
and se
Howev
of feed
decrea
hypon
altere

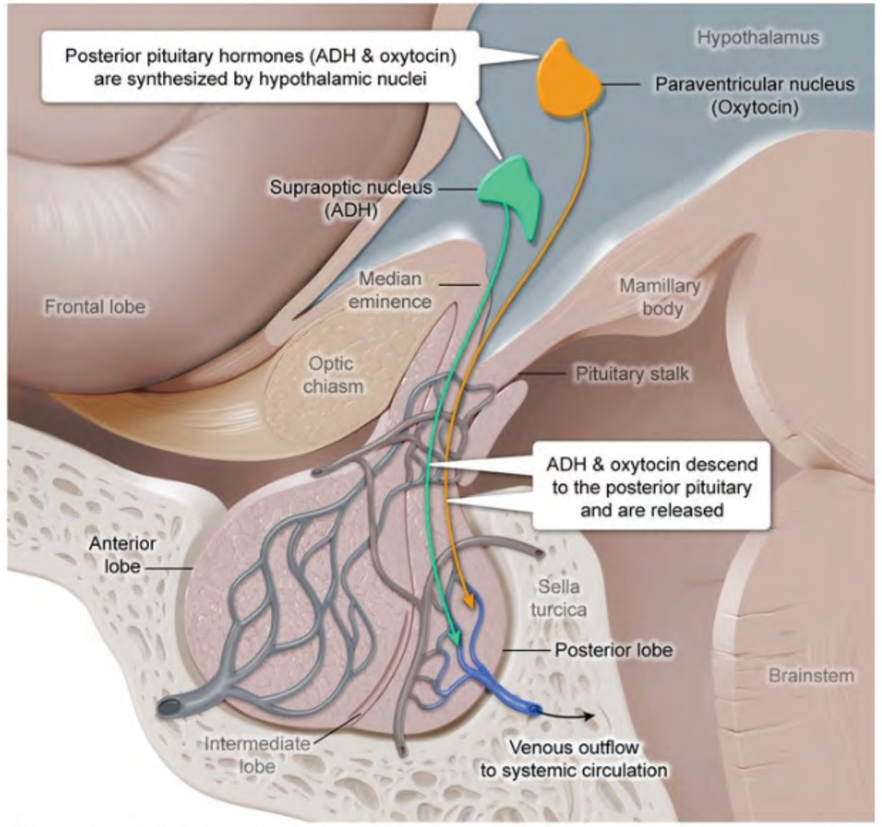
In SIA
hyperv
stimula
result,
(**euvol**
jugular

(Choi
degree
approp

Educa
The sy
osmola
import

Pathoph
Subject

Posterior pituitary (neurohypophysis)



ADH = Antidiuretic hormone (ie, vasopressin).

©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Copyright © UWorld. All rights reserved.

https://t.me/USMLEWorldStep1

A 64-year-old woman is brought to the emergency department due to confusion and lethargy. The patient was asymptomatic when her husband left for work in the morning, but when he arrived home, he found her in bed, weak and disoriented. The patient's medical conditions include type 2 diabetes mellitus and hypertension, for which she takes multiple medications. She does not use tobacco, alcohol, or recreational drugs. Temperature is 37 C (98.6 F), blood pressure is 140/70 mm Hg, pulse is 74/min, and respirations are 18/min. On physical examination, the patient is somnolent but withdraws all extremities to pain. Laboratory testing shows an elevated serum C-peptide level. If this patient's current condition is due to an antidiabetic drug, which of the following is the most likely culprit agent?

- A. Acarbose
- B. Canagliflozin
- C. Glyburide
- D. Long-acting insulin
- E. Metformin
- F. Pioglitazone
- G. Short-acting insulin

Submit

https://t.me/USMLEWorldStep1

A 64-year-old woman is brought to the emergency department due to confusion and lethargy. The patient was asymptomatic when her husband left for work in the morning, but when he arrived home, he found her in bed, weak and disoriented. The patient's medical conditions include type 2 diabetes mellitus and hypertension, for which she takes multiple medications. She does not use tobacco, alcohol, or recreational drugs. Temperature is 37 C (98.6 F), blood pressure is 140/70 mm Hg, pulse is 74/min, and respirations are 18/min. On physical examination, the patient is somnolent but withdraws all extremities to pain. Laboratory testing shows an elevated serum C-peptide level. If this patient's current condition is due to an antidiabetic drug, which of the following is the most likely culprit agent?

- ✗ A. Acarbose (1%)
- B. Canagliflozin (4%)
- ✓ C. Glyburide (64%)
- D. Long-acting insulin (7%)
- E. Metformin (6%)
- F. Pioglitazone (8%)
- G. Short-acting insulin (7%)

Incorrect
Correct answer
C

64%
Answered correctly

03 secs
Time Spent

2023
Version

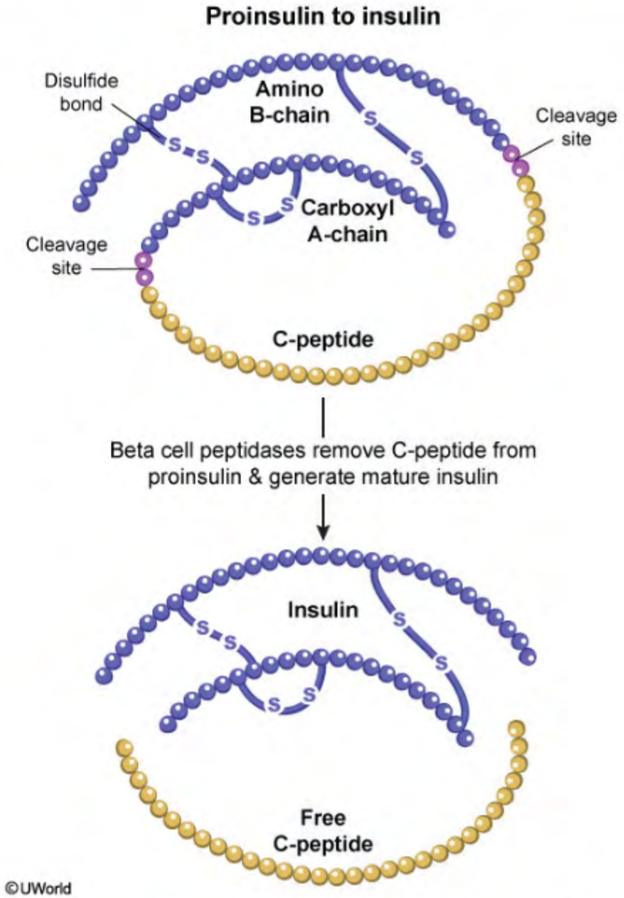
Explanation



https://t.me/USMLEWorldStep1

D. Long-acting insulin (7%)

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

©UWorld

This patient with type 2 diabetes mellitus has acute confusion and lethargy, findings consistent with symptomatic **hypoglycemia**, a common adverse effect of certain antidiabetic medications. Her **elevated C-peptide** level further indicates a medication that stimulates **endogenous** pancreatic insulin secretion independent of blood glucose levels, such as **sulfonylureas** (eg, glyburide) or meglitinides.

Insulin is synthesized in pancreatic beta cells as preproinsulin, which is guided by a signal peptide into the rough endoplasmic reticulum during translation. The signal peptide is then removed, converting preproinsulin to proinsulin. Protein folding and disulfide bond formation take place as proinsulin traverses the rough endoplasmic reticulum. Proinsulin is then transported to the Golgi apparatus, where it is packaged with proteolytic enzymes into insulin secretory granules and cleaved into mature insulin and C-peptide. **C-peptide and insulin** are then **cosecreted** from pancreatic beta cells in equimolar amounts.

When hypoglycemia is due to excessive endogenous insulin production (eg, sulfonylureas, meglitinides, insulinoma), C-peptide levels are elevated. In contrast, **exogenous insulin** and insulin analogues (ie, insulin-like polypeptides with structural alterations to optimize pharmacokinetic properties) **do not contain C-peptide**. When hypoglycemia is induced by these agents, endogenous insulin secretion is suppressed and C-peptide levels are low **(Choices D and G)**.

(Choice A) Acarbose inhibits alpha-glucosidase in the intestinal brush border, impairing the hydrolysis of polymeric carbohydrates and leading to decreased postprandial glucose absorption. Acarbose indirectly decreases endogenous insulin (and C-peptide) secretion by reducing postprandial hyperglycemia.

(Choices B, E, and F) Sodium-glucose cotransporter-2 inhibitors (eg, canagliflozin, dapagliflozin) act in the kidney to decrease the reabsorption of filtered glucose. Metformin decreases hepatic glucose production and increases peripheral glucose uptake and use. Thiazolidinediones (eg, pioglitazone) increase insulin sensitivity. These agents do not increase endogenous insulin secretion and therefore do not elevate the C-peptide level.

Educational objective:
Proinsulin is cleaved into insulin and C-peptide; therefore, C-peptide is a marker of endogenous insulin secretion. Diabetic medications that increase endogenous insulin secretion (eg, sulfonylureas) elevate the C-peptide level.

References

https://t.me/USMLEWorldStep1

A 34-year-old man comes to the office due to a 6-month history of progressively worsening headaches. He has also noticed blurring of his peripheral vision while driving. The patient has no history of head injuries and has had no associated dizziness, weight change, diplopia, or polyuria. Medical history is unremarkable, and he takes no medications. He does not use tobacco, alcohol, or illicit drugs. Physical examination shows a bitemporal visual field deficit. Laboratory studies show a serum prolactin level >20 times the upper limit of normal. Cranial imaging reveals a large pituitary mass. Which of the following changes in serum GnRH, LH, and testosterone are most likely to be found in this patient?

	GnRH	LH	Testosterone
○ A.	↓	↓	↓
○ B.	↑	↓	↓
○ C.	↑	↑	↓
○ D.	↑	↑	↑
○ E.	↓	↓	↑

Submit

https://t.me/USMLEWorldStep1

A 34-year-old man comes to the office due to a 6-month history of progressively worsening headaches. He has also noticed blurring of his peripheral vision while driving. The patient has no history of head injuries and has had no associated dizziness, weight change, diplopia, or polyuria. Medical history is unremarkable, and he takes no medications. He does not use tobacco, alcohol, or illicit drugs. Physical examination shows a bitemporal visual field deficit. Laboratory studies show a serum prolactin level >20 times the upper limit of normal. Cranial imaging reveals a large pituitary mass. Which of the following changes in serum GnRH, LH, and testosterone are most likely to be found in this patient?

	GnRH	LH	Testosterone	
✓ A.	↓	↓	↓	(68%)
B.	↑	↓	↓	(18%)
C.	↑	↑	↓	(4%)
D.	↑	↑	↑	(4%)
E.	↓	↓	↑	(3%)

Correct

68% Answered correctly

03 secs Time Spent

2023 Version

Explanation

Pituitary adenomas	
Cell type	**Clinical features of tumor**
Lactotroph (prolactin)	• Hypogonadism, infertility (men) • Galactorrhea, amenorrhea (women)

https://t.me/USMLEWorldStep1

Pituitary adenomas	
Cell type	**Clinical features of tumor**
Lactotroph (prolactin)	• Hypogonadism, infertility (men) • Galactorrhea, amenorrhea (women)
Corticotroph (ACTH)	• Cushing disease
Somatotroph (growth hormone)	• Acromegaly (adults) • Gigantism (children)
Thyrotroph (TSH)	• Thyrotoxicosis
Gonadotroph (LH, FSH)	• Nonfunctioning (hypopituitarism) • Mass effect

This patient's **bitemporal hemianopsia** and headaches suggest mass effect symptoms due to an expanding lesion near the optic chiasm. Cranial imaging (typically MRI scan) can confirm the diagnosis of a pituitary adenoma. Unlike other pituitary hormones, prolactin secretion is under negative regulation by dopamine from the hypothalamus, and any disruption of dopaminergic pathways in the pituitary stalk can cause a moderate increase in prolactin release. However, **very high prolactin levels**, as seen in this patient, suggest a prolactin-secreting adenoma (**prolactinoma**).

Increased circulating levels of prolactin suppress GnRH secretion, leading to a reduction in release of LH from the pituitary and decreased testicular testosterone production. In premenopausal women, prolactinomas typically present early with galactorrhea and amenorrhea. However, in men and postmenopausal women, early symptoms may be subtle and nonspecific (eg, decreased libido), and patients frequently present later with mass effect symptoms (eg, headache, visual field defects).

(Choices B and D) Physiologic GnRH secretion occurs in a pulsatile fashion and initiates gonadotropin (eg, LH,

https://t.me/USMLEWorldStep1

Gonadotroph (LH, FSH)	• Nonfunctioning (hypopituitarism) • Mass effect

This patient's **bitemporal hemianopsia** and headaches suggest mass effect symptoms due to an expanding lesion near the optic chiasm. Cranial imaging (typically MRI scan) can confirm the diagnosis of a pituitary adenoma. Unlike other pituitary hormones, prolactin secretion is under negative regulation by dopamine from the hypothalamus, and any disruption of dopaminergic pathways in the pituitary stalk can cause a moderate increase in prolactin release. However, **very high prolactin levels**, as seen in this patient, suggest a prolactin-secreting adenoma (**prolactinoma**).

Increased circulating levels of prolactin suppress GnRH secretion, leading to a reduction in release of LH from the pituitary and decreased testicular testosterone production. In premenopausal women, prolactinomas typically present early with galactorrhea and amenorrhea. However, in men and postmenopausal women, early symptoms may be subtle and nonspecific (eg, decreased libido), and patients frequently present later with mass effect symptoms (eg, headache, visual field defects).

(Choices B and D) Physiologic GnRH secretion occurs in a pulsatile fashion and initiates gonadotropin (eg, LH, FSH) and subsequently testosterone secretion. However, prolonged, continuous GnRH secretion suppresses gonadotropins, resulting in lower levels of sex steroids. Long-acting GnRH agonists (eg, leuprolide) are used to suppress sex steroid–dependent diseases (eg, prostate cancer).

(Choice C) Primary hypogonadism with low testosterone levels results in loss of negative feedback on GnRH release, causing elevated levels of GnRH and LH.

(Choice E) Intake of exogenous testosterone (eg, anabolic steroid use) will suppress release of GnRH and subsequently LH.

Educational objective:
Large prolactin-secreting pituitary tumors can compress the optic chiasm, causing bitemporal hemianopsia. In addition, elevated prolactin levels suppress release of GnRH, leading to decreased LH secretion and subsequently impaired testosterone production in men.

References

https://t.me/USMLEWorldStep1

Gonadotroph (LH, FSH)	• Nonfunctioning (hypopituitarism) • Mass effect

This p
lesion
adeno
hypoth
in prol
adeno

Increa
pituita
preser
may b
sympt

(Choi
FSH) a
gonad
suppre

(Choi
releas

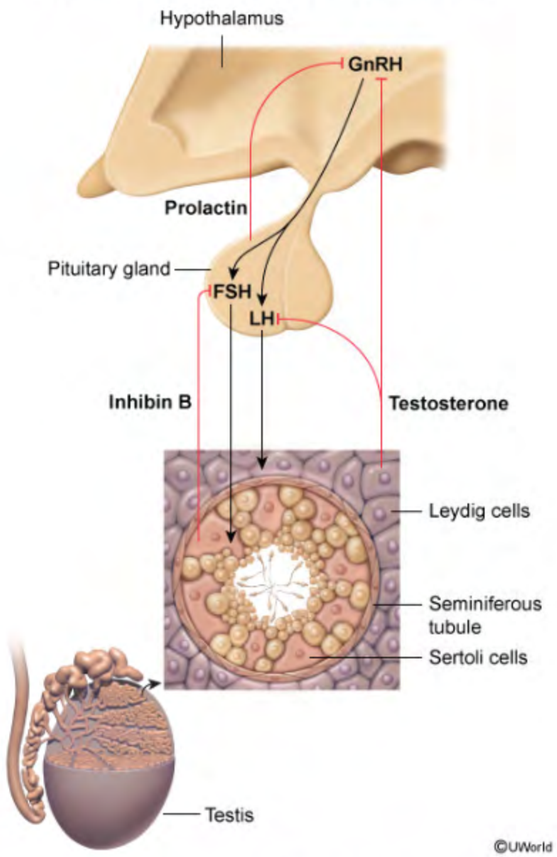
(Choi
subse

Educa
Large
additic
impair

References

Exhibit Display

Prolactin and gonadotropin production



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

A 2-year-old girl is brought to the clinic by her mother for evaluation of ambiguous genitalia. She was born with clitoral enlargement and partial fusion of the labioscrotal folds. The patient has also had high blood pressure recorded on 3 consecutive office visits. She has been tracking at the 50th percentile for height and weight, and has not had any other medical problems. Family history is noncontributory. Laboratory studies are significant for moderate hypokalemia. Cytogenetic studies show a 46,XX karyotype. Which of the following enzymes is most likely deficient in this patient?

- A. 5α-reductase
- B. 11β-hydroxylase
- C. 17α-hydroxylase
- D. 21-hydroxylase
- E. Side-chain cleavage enzyme

Submit

https://t.me/USMLEWorldStep1

A 2-year-old girl is brought to the clinic by her mother for evaluation of ambiguous genitalia. She was born with clitoral enlargement and partial fusion of the labioscrotal folds. The patient has also had high blood pressure recorded on 3 consecutive office visits. She has been tracking at the 50th percentile for height and weight, and has not had any other medical problems. Family history is noncontributory. Laboratory studies are significant for moderate hypokalemia. Cytogenetic studies show a 46,XX karyotype. Which of the following enzymes is most likely deficient in this patient?

- ✗ A. 5α-reductase (1%)
- ✓ B. 11β-hydroxylase (56%)
- C. 17α-hydroxylase (21%)
- D. 21-hydroxylase (20%)
- E. Side-chain cleavage enzyme (0%)

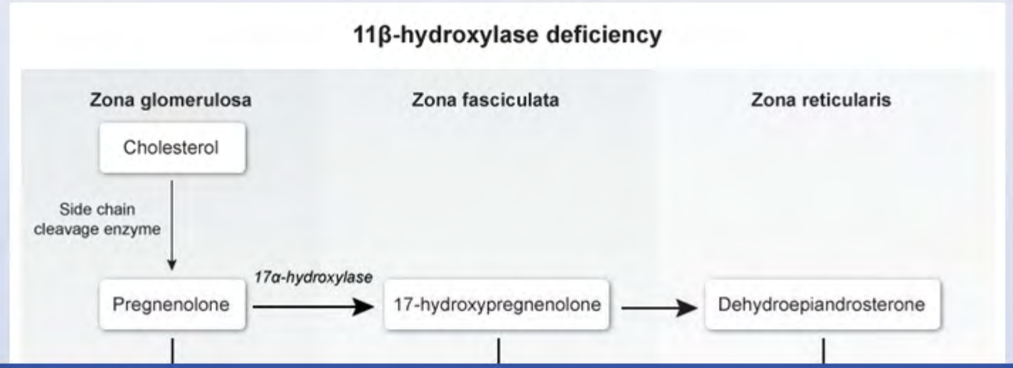
Incorrect
Correct answer
B

56%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation



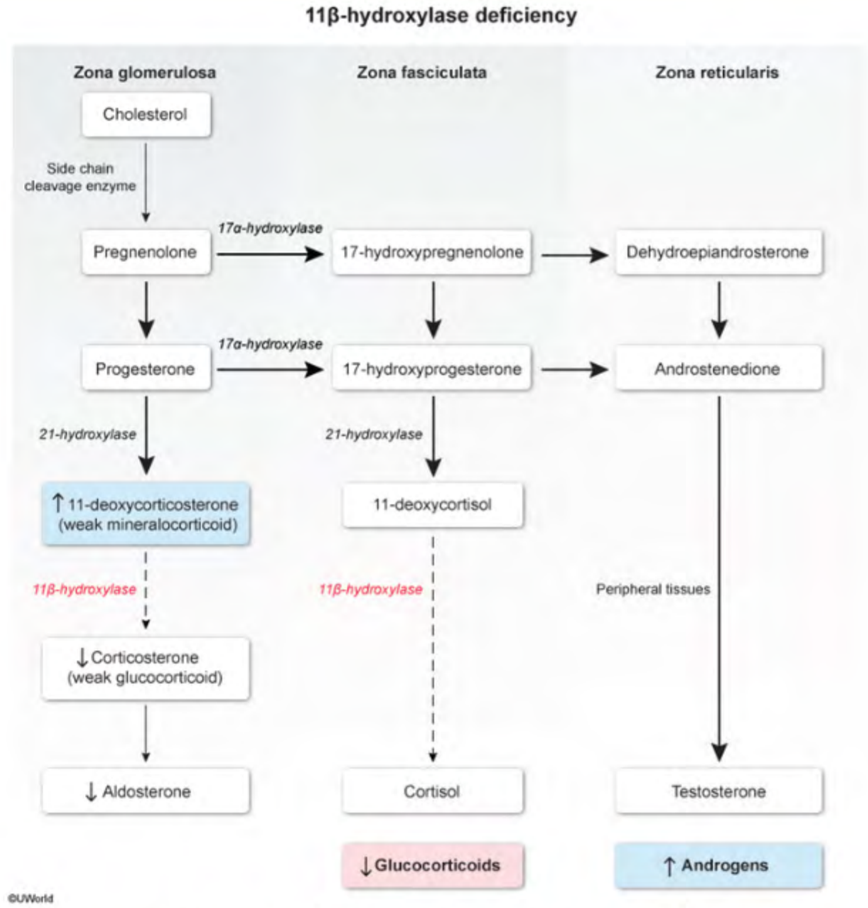
https://t.me/USMLEWorldStep1

A 2-year-old girl is brought to the clinic by her mother for evaluation of ambiguous genitalia. She was born with clitoral
record
has no
moder
likely c

Incc
Corre
B

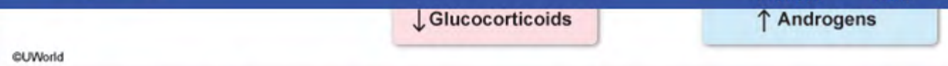
Expl

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1



This girl with ambiguous genitalia, hypertension, and hypokalemia most likely has **11β-hydroxylase deficiency**, the second-most common cause of congenital adrenal hyperplasia after 21-hydroxylase deficiency.

11β-hydroxylase is responsible for converting 11-deoxycorticosterone to corticosterone and 11-deoxycortisol to cortisol. Enzyme deficiency results in the buildup of aldosterone and cortisol precursors, which are then shunted toward adrenal androgen synthesis. In genetically female infants, **androgen excess** leads to **ambiguous genitalia** (virilization). Although 11β-hydroxylase deficiency inhibits aldosterone synthesis, **11-deoxycorticosterone** accumulates and acts as a weak mineralocorticoid, causing affected individuals to have **hypertension** and **hypokalemia**.

(Choice A) 5α-reductase deficiency causes ambiguous genitalia in boys due to the defective conversion of testosterone to dihydrotestosterone. Girls have normal genitalia, and blood pressure and electrolytes are unaffected.

(Choice C) 17α-hydroxylase deficiency results in impaired sex steroid and cortisol synthesis, and increased production of mineralocorticoids. Girls are born with normal genitalia, but boys are born undervirilized (ambiguous genitalia). Affected individuals develop hypertension and hypokalemia (mineralocorticoid excess) and do not undergo puberty (no sex steroids).

(Choice D) 21-hydroxylase deficiency decreases glucocorticoid and mineralocorticoid synthesis and increases adrenal androgen production. Girls are born with ambiguous genitalia (androgen excess) and frequently develop hypotension and hyperkalemia (mineralocorticoid deficiency).

(Choice E) Side-chain cleavage enzyme converts cholesterol to pregnenolone. Because this is the first enzyme in the steroidogenic pathway, deficiency impairs synthesis of all steroid hormones. Complete deficiency is lethal due to absent placental progesterone synthesis.

Educational objective:
11β-hydroxylase deficiency typically results in excessive adrenal androgen and mineralocorticoid (11-deoxycorticosterone) production. Genetically female infants are born with ambiguous genitalia, and affected individuals develop hypertension and hypokalemia early in life.

https://t.me/USMLEWorldStep1

↓Glucocorticoids
↑Androgens

©UWorld

This g
the se

11β-hy
cortisc
towarc
genita
deoxy
hyper

(Choi
testost
unaffe

(Choi
produc
genita
underg

(Choi
adrena
hypote

(Choi
in the
due to

Educa
11β-hy
deoxycorticosterone) production. Genetically female infants are born with ambiguous genitalia, and affected individuals develop hypertension and hypokalemia early in life.

Exhibit Display

Congenital adrenal hyperplasia				
Enzyme deficiency	**Mineralocorticoids**	**Glucocorticoids**	**Androgens**	**Symptoms**
21-Hydroxylase	↓	↓	↑	• Salt wasting (vomiting, hypotension, ↓ Na^+, ↑ K^+) • Ambiguous genitalia in girls
11β-Hydroxylase	↑*	↓	↑	• Hypertension, ↓ K^+ • Ambiguous genitalia in girls
17α-Hydroxylase	↑	↑**	↓	• Hypertension, ↓ K^+ • Ambiguous genitalia in boys • Absent puberty

*Low aldosterone but excessive, weak mineralocorticoid (11-deoxycorticosterone).
**Low cortisol but excessive, weak glucocorticoid (corticosterone).

New | Existing | My Notebook

https://t.me/USMLEWorldStep1

↓Glucocorticoids
↑Androgens

©UWorld

This g
the se

11β-hy
cortisc
toward
genita
deoxy
hyper

(Choi
testost
unaffe

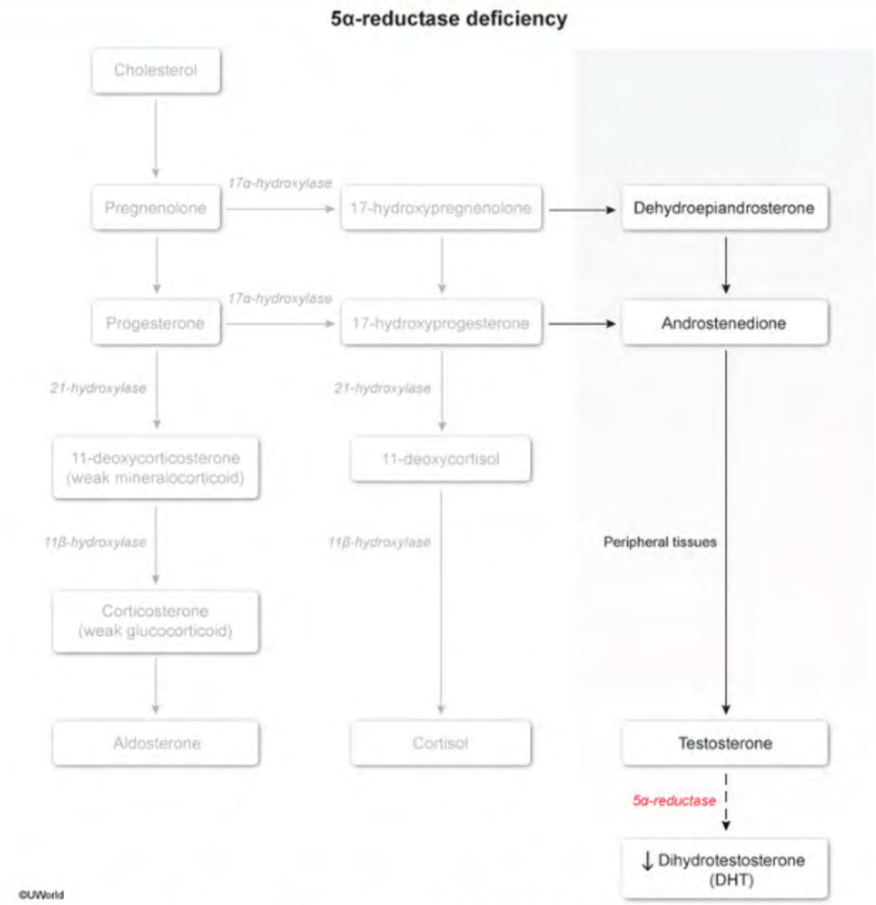
(Choi
produc
genita
underg

(Choi
adrena
hypote

(Choi
in the
due to

Educa
11β-hy
deoxycorticosterone) production. Genetically female infants are born with ambiguous genitalia, and affected individuals develop hypertension and hypokalemia early in life.

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

↓Glucocorticoids ↑Androgens

©UWorld

This g
the se

11β-hy
cortisc
toward
genita
deoxy
hyper

(Choi
testost
unaffe

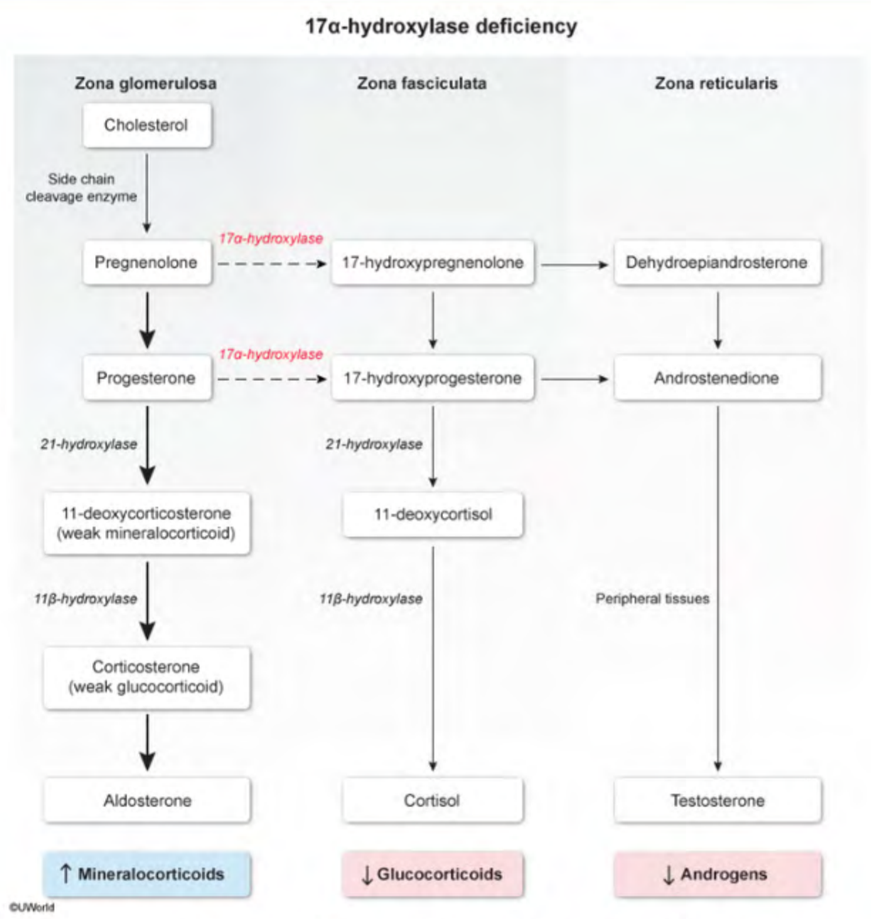
(Choi
produc
genita
underg

(Choi
adrena
hypote

(Choi
in the
due to

Educa
11β-hy
deoxy
individuals develop hypertension and hypokalemia early in life.

Exhibit Display



Zoom In Zoom Out Reset New | Existing My Notebook

https://t.me/USMLEWorldStep1

↓Glucocorticoids ↑Androgens

©UWorld

This g
the se

11β-hy
cortisc
toward
genita
deoxy
hyper

(Choi
testost
unaffe

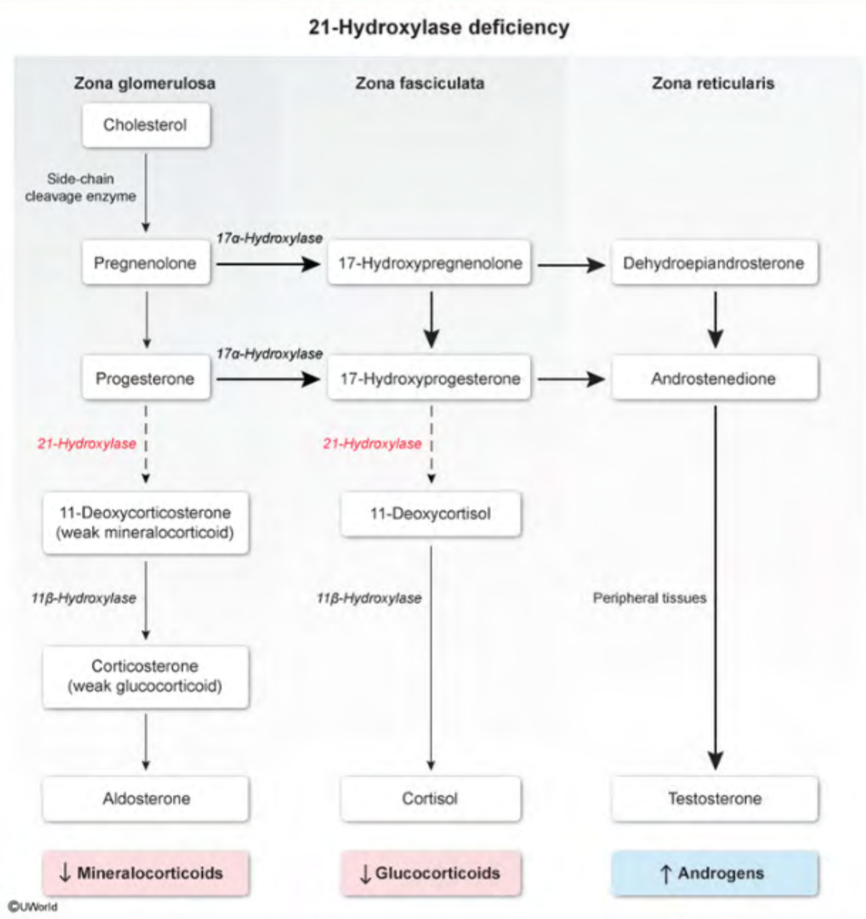
(Choi
produc
genita
underg

(Choi
adrena
hypote

(Choi
in the
due to

Educa
11β-hy
deoxy
individuals develop hypertension and hypokalemia early in life.

Exhibit Display



Zoom In Zoom Out Reset New | Existing My Notebook

https://t.me/USMLEWorldStep1

A 25-year-old woman comes to the office because of jitteriness, frequent mood swings, and palpitations for the past 2 months. At times, her symptoms make her worry that she may be having a heart attack. The patient has no prior medical conditions. Temperature is 37 C (98.6 F), blood pressure is 120/82 mm Hg, pulse is 102/min, and respirations are 12/min. Examination shows warm, moist skin and a fine tremor of the fingers. Which of the following would most likely provide the fastest relief of this patient's symptoms?

- A. Fluoxetine
- B. Methimazole
- C. Prazosin
- D. Propranolol
- E. Radioactive iodine

Submit

https://t.me/USMLEWorldStep1

A 25-year-old woman comes to the office because of jitteriness, frequent mood swings, and palpitations for the past 2 months. At times, her symptoms make her worry that she may be having a heart attack. The patient has no prior medical conditions. Temperature is 37 C (98.6 F), blood pressure is 120/82 mm Hg, pulse is 102/min, and respirations are 12/min. Examination shows warm, moist skin and a fine tremor of the fingers. Which of the following would most likely provide the fastest relief of this patient's symptoms?

- ✗ A. Fluoxetine (3%)
- B. Methimazole (8%)
- C. Prazosin (1%)
- ✓ D. Propranolol (83%)
- E. Radioactive iodine (3%)

Incorrect
Correct answer
D

83%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

General manifestations of hyperthyroidism	
Symptoms	• Anxiety & insomnia • Palpitations • Heat intolerance • Increased perspiration • Weight loss without decreased appetite
	• Goiter

https://t.me/USMLEWorldStep1

Explanation

General manifestations of hyperthyroidism	
Symptoms	• Anxiety & insomnia • Palpitations • Heat intolerance • Increased perspiration • Weight loss without decreased appetite
Physical examination	• Goiter • Hypertension • Tremors involving fingers/hands • Hyperreflexia • Proximal muscle weakness • Lid lag • Atrial fibrillation

This patient has signs and symptoms of **thyrotoxicosis**, including tremor, dysphoria, sweating, and tachycardia with palpitations. Hyperthyroidism is associated with **upregulation of beta-adrenergic receptors** and increased adrenergic tone, which is responsible for many of the associated clinical features.

Beta-adrenergic antagonists (eg, propranolol) are indicated to **alleviate the adrenergic symptoms** of thyrotoxicosis and are usually prescribed early, while completing the diagnostic evaluation and initiating definitive management (eg, antithyroid medication, radioiodine ablation, thyroidectomy). Some beta-adrenergic antagonists (eg, propranolol) also reduce peripheral conversion of thyroxine (T4) to triiodothyronine (T3), although this effect is delayed.

(Choice A) Fluoxetine is a selective serotonin reuptake inhibitor (SSRI) used to treat anxiety or depression. This patient's anxiety and mood symptoms will likely resolve with treatment of the underlying condition (ie,

https://t.me/USMLEWorldStep1

	• Atrial fibrillation

This patient has signs and symptoms of **thyrotoxicosis**, including tremor, dysphoria, sweating, and tachycardia with palpitations. Hyperthyroidism is associated with **upregulation of beta-adrenergic receptors** and increased adrenergic tone, which is responsible for many of the associated clinical features.

Beta-adrenergic antagonists (eg, propranolol) are indicated to **alleviate the adrenergic symptoms** of thyrotoxicosis and are usually prescribed early, while completing the diagnostic evaluation and initiating definitive management (eg, antithyroid medication, radioiodine ablation, thyroidectomy). Some beta-adrenergic antagonists (eg, propranolol) also reduce peripheral conversion of thyroxine (T4) to triiodothyronine (T3), although this effect is delayed.

(Choice A) Fluoxetine is a selective serotonin reuptake inhibitor (SSRI) used to treat anxiety or depression. This patient's anxiety and mood symptoms will likely resolve with treatment of the underlying condition (ie, thyrotoxicosis). Also, SSRIs typically require 2-4 weeks for a noticeable effect.

(Choice B) Thioamides (eg, methimazole, propylthiouracil) reduce the production of thyroid hormone by inhibiting thyroperoxidase, the enzyme responsible for iodination of tyrosine residues in follicular colloid. Although these agents are indicated for the treatment of hyperthyroidism due to overproduction of thyroid hormone (eg, Graves disease), they produce clinical effects only after a few weeks.

(Choice C) Prazosin is an alpha-1 adrenergic antagonist. Alpha-1 adrenergic receptors are present on the vasculature and induce vasoconstriction when stimulated. Blockade of these receptors would not alleviate the patient's palpitations and tremor.

(Choice E) Radioactive iodine is used to treat a variety of hyperthyroid disorders, most commonly Graves disease, but it takes several weeks to be effective. In addition, it occasionally causes a paradoxical increase in thyroid hormone production early in treatment (jod-Basedow effect) and therefore should be administered with beta-adrenergic antagonists.

Educational objective:
Beta blockers provide rapid relief of the adrenergic-mediated symptoms of thyrotoxicosis and can be given while awaiting diagnostic evaluation and definitive management.

https://t.me/USMLEWorldStep1

An 18-month-old boy is being evaluated for neurologic regression. He had a normal neonatal course and early development until age 5 months. The boy subsequently experienced gradual regression of developmental milestones, and now has inability to sit with support, poor head control, and loss of a social smile. Weight and height are below the 5th percentile. Physical examination shows an enlarged liver and spleen, diminished deep tendon reflexes in all limbs, and hypotonia. Funduscopic findings are shown in the exhibit. This patient most likely has an accumulation of which of the following substrates?

- A. Cerebroside sulfate
- B. Galactocerebroside
- C. Globotriaosylceramide
- D. Glucocerebroside
- E. GM2 ganglioside
- F. Sphingomyelin

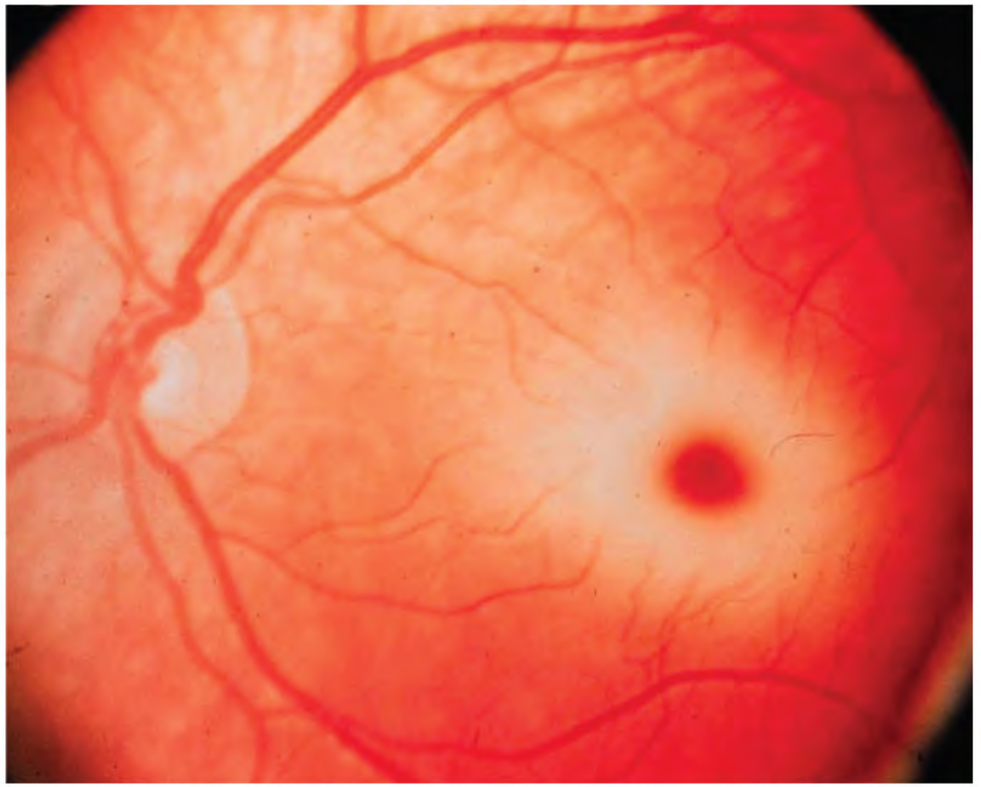
Submit

https://t.me/USMLEWorldStep1

An 18-month-old boy is being evaluated for neurologic regression. He had a normal neonatal course and early
develo
milest
height
tendor
has ar

Sub

Exhibit Display



Zoom In Zoom Out Reset New | Existing My Notebook

https://t.me/USMLEWorldStep1

An 18-month-old boy is being evaluated for neurologic regression. He had a normal neonatal course and early development until age 5 months. The boy subsequently experienced gradual regression of developmental milestones, and now has inability to sit with support, poor head control, and loss of a social smile. Weight and height are below the 5th percentile. Physical examination shows an enlarged liver and spleen, diminished deep tendon reflexes in all limbs, and hypotonia. Funduscopic findings are shown in the exhibit. This patient most likely has an accumulation of which of the following substrates?

- A. Cerebroside sulfate (1%)
- ✕ B. Galactocerebroside (10%)
- C. Globotriaosylceramide (0%)
- D. Glucocerebroside (7%)
- E. GM2 ganglioside (17%)
- ✓ F. Sphingomyelin (62%)

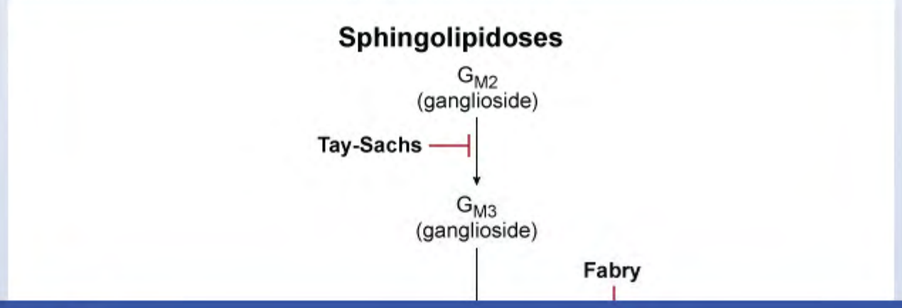
Incorrect
Correct answer
F

62%
Answered correctly

34 secs
Time Spent

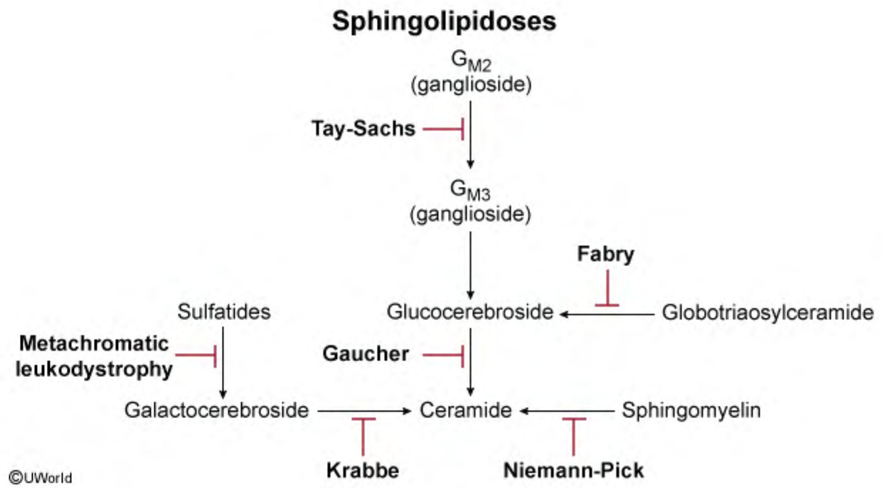
2023
Version

Explanation



https://t.me/USMLEWorldStep1

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Niema
by **sph**
constit
in cells
accum
respon
milest

This p
neurol

(Choi
sulfate
neurop

(Choice B) In Krabbe disease, galactocerebrosidase deficiency causes accumulation of galactocerebroside and psychosine. Infants have developmental delay and/or regression, axial hypotonia, limb stiffness, optic atrophy, and

https://t.me/USMLEWorldStep1

Niemann-Pick disease is an autosomal recessive disorder common among Ashkenazi Jews and is characterized by **sphingomyelinase deficiency**. Sphingomyelinase is responsible for the breakdown of sphingomyelin, a lipid constituent of cell membranes. In Niemann-Pick disease, **sphingomyelin accumulation** within lysosomes results in cells that appear enlarged, foamy, and vacuolated on electron microscopy. These lipid-laden foam cells accumulate in the liver and spleen and cause **hepatosplenomegaly**. Progressive neuronal accumulation is responsible for **hypotonia** and **neurologic degeneration** (eg, failure to progress developmentally, loss of milestones). Retinal accumulation leads to a cherry-red macular spot.

This patient is presenting with the classic infantile type A variant that results in hepatosplenomegaly, progressive neurologic deterioration, and death by age 3 years.

(Choice A) In patients with metachromatic leukodystrophy, central nervous system accumulation of cerebroside sulfate is caused by arylsulfatase A deficiency. Central and peripheral demyelination leads to peripheral neuropathy and ataxia.

(Choice B) In Krabbe disease, galactocerebrosidase deficiency causes accumulation of galactocerebroside and psychosine. Infants have developmental delay and/or regression, axial hypotonia, limb stiffness, optic atrophy, and seizures.

(Choice C) In Fabry disease, α-galactosidase A deficiency causes globotriaosylceramide (ceramide trihexoside) accumulation. Clinical manifestations begin in childhood with neuropathic pain and dermatologic pathology (eg, telangiectasias, angiokeratomas).

(Choice D) Glucocerebroside accumulation occurs in Gaucher disease, an autosomal recessive disorder of β-glucocerebrosidase deficiency. Patients typically have hepatosplenomegaly, pancytopenia, and skeletal problems.

(Choice E) Patients with Tay-Sachs disease are deficient in β-hexosaminidase A, which leads to GM2 accumulation in neurons. Neurologic regression and cherry-red macular spots are classic symptoms (similar to Niemann-Pick disease), but hepatosplenomegaly is absent.

Educational objective:
In Niemann-Pick disease, sphingomyelinase deficiency causes accumulation of the lipid sphingomyelin. Clinical features include hepatosplenomegaly, neurologic regression, and a cherry-red macular spot in infancy.

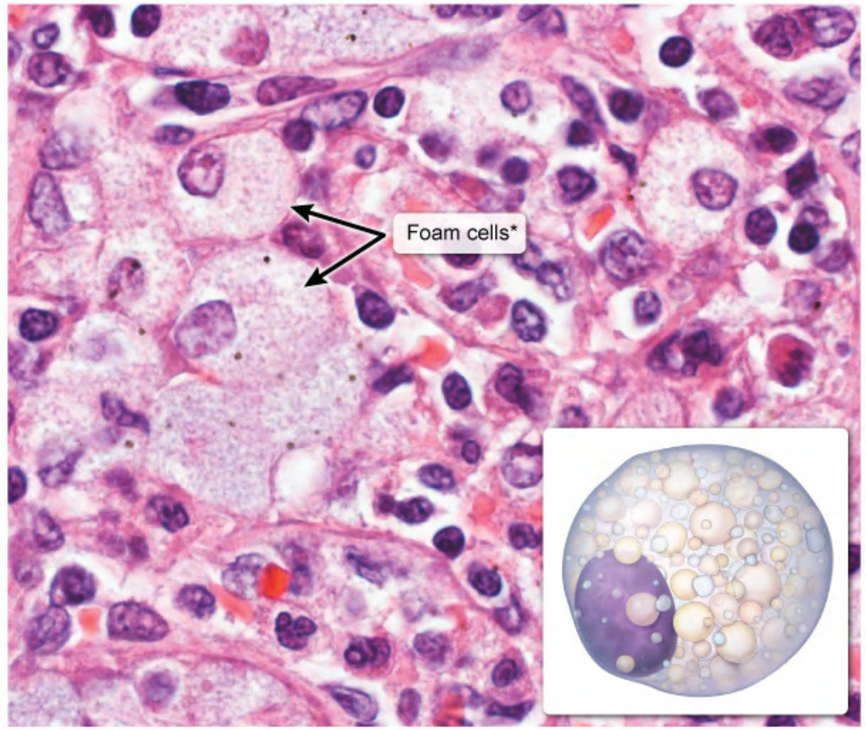
https://t.me/USMLEWorldStep1

(ganglioside)

Fabry

Exhibit Display

Niemann-Pick disease



*Macrophages with foamy cytoplasm due to sphingomyelin accumulation in lysosomes.

©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Niema
by sph
constit
in cells
accum
respon
milest

This p
neurol

(Choic
sulfate
neurop

(Choic
psych
seizur

(Choic
accum
telang

(Choice D) Glucocerebroside accumulation occurs in Gaucher disease, an autosomal recessive disorder of β-glucocerebrosidase deficiency. Patients typically have hepatosplenomegaly, pancytopenia, and skeletal problems.

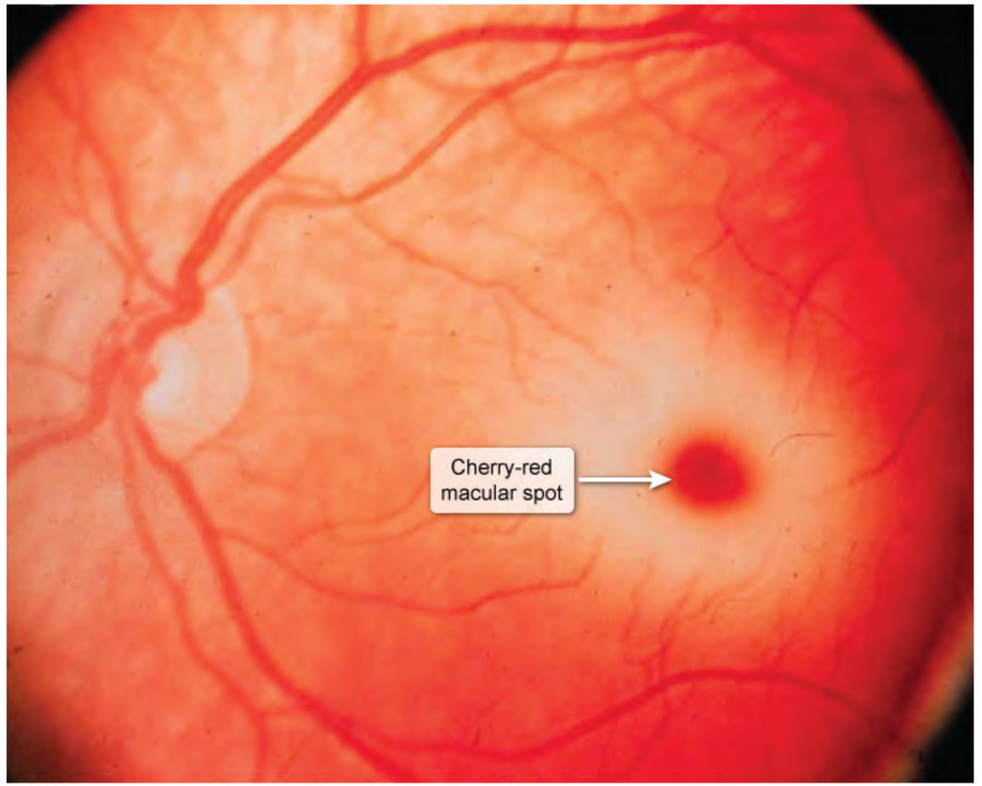
https://t.me/USMLEWorldStep1

(ganglioside)

Fabry

Exhibit Display

Cherry-red macular spot



©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Niema
by sph
constit
in cells
accum
respon
milest

This p
neurol

(Choic
sulfate
neurop

(Choic
psych
seizur

(Choic
accum
telang

(Choice D) Glucocerebroside accumulation occurs in Gaucher disease, an autosomal recessive disorder of β-glucocerebrosidase deficiency. Patients typically have hepatosplenomegaly, pancytopenia, and skeletal problems.

https://t.me/USMLEWorldStep1

A newborn boy is found to have a serum TSH above and serum thyroxine below the normal range for his age. The patient was born at 39 weeks gestation via spontaneous vaginal delivery. His mother has no medical conditions. On examination, the patient's length and weight are normal, and he has no apparent congenital abnormalities. Ultrasound of the neck shows a normal-sized thyroid gland in the appropriate location. Which of the following is the most likely cause of this patient's condition?

- A. Central hypothyroidism
- B. Generalized resistance to thyroid hormones
- C. Thyroid gland resistance to TSH
- D. Thyroid hormone–binding globulin deficiency
- E. TSH receptor–stimulating antibodies

Submit

https://t.me/USMLEWorldStep1

A newborn boy is found to have a serum TSH above and serum thyroxine below the normal range for his age. The patient was born at 39 weeks gestation via spontaneous vaginal delivery. His mother has no medical conditions. On examination, the patient's length and weight are normal, and he has no apparent congenital abnormalities. Ultrasound of the neck shows a normal-sized thyroid gland in the appropriate location. Which of the following is the most likely cause of this patient's condition?

- A. Central hypothyroidism
- B. Generalized resistance to thyroid hormones
- C. Thyroid gland resistance to TSH
- D. Thyroid hormone–binding globulin deficiency
- E. TSH receptor–stimulating antibodies

Submit

https://t.me/USMLEWorldStep1

A newborn boy is found to have a serum TSH above and serum thyroxine below the normal range for his age. The patient was born at 39 weeks gestation via spontaneous vaginal delivery. His mother has no medical conditions. On examination, the patient's length and weight are normal, and he has no apparent congenital abnormalities. Ultrasound of the neck shows a normal-sized thyroid gland in the appropriate location. Which of the following is the most likely cause of this patient's condition?

- A. Central hypothyroidism (10%)
- ✗ B. Generalized resistance to thyroid hormones (4%)
- ✓ C. Thyroid gland resistance to TSH (61%)
- D. Thyroid hormone–binding globulin deficiency (18%)
- E. TSH receptor–stimulating antibodies (5%)

Incorrect
Correct answer
C

61%
Answered correctly

31 secs
Time Spent

2023
Version

Explanation

Congenital hypothyroidism		
Cause	**Free & total T4**	**TSH**
• Primary hypothyroidism ◦ Thyroid dysgenesis ◦ TSH resistance	↓	↑
• Thyroid hormone resistance	↑	↑
• Central hypothyroidism	↓	↓

https://t.me/USMLEWorldStep1

Congenital hypothyroidism		
Cause	**Free & total T4**	**TSH**
• Primary hypothyroidism ○ Thyroid dysgenesis ○ TSH resistance	↓	↑
• Thyroid hormone resistance	↑	↑
• Central hypothyroidism	↓	↓
• Transient due to maternal exposure ○ Iodine excess or deficiency ○ TSH receptor–blocking antibodies ○ Antithyroid medications	↓	↑
T4 = thyroxine.		

This patient has an **elevated serum TSH** and **decreased thyroxine (T4) level**, findings consistent with **primary hypothyroidism**. The most common congenital causes are thyroid dysgenesis (eg, ectopy, hypoplasia) and TSH resistance. Less common, transient etiologies are usually due to maternal conditions (eg, iodine excess, antithyroid medications). Given that this patient's **thyroid is normal in size and location** and the mother has no medical conditions, the most likely cause is thyroid gland resistance to TSH.

TSH is normally produced by the anterior pituitary and binds to TSH receptors on follicular thyroid cells to stimulate T4 production. In TSH resistance, a **mutation in the TSH receptor gene** leads to thyroid insensitivity to TSH and reduced synthesis of T4. Low T4 leads to positive feedback to the pituitary, further increasing TSH levels.

Newborns are usually asymptomatic due to placentally transferred maternal T4 (although thyroid hormones do not readily cross the placenta, enough T4 can usually cross to prevent development of overt symptoms); diagnosis is typically via newborn screening. Treatment is lifelong levothyroxine.

(Choice A) Central hypothyroidism (eg, panhypopituitarism) causes low serum T4 due to decreased production of

https://t.me/USMLEWorldStep1

○ Antithyroid medications		
T4 = thyroxine.		

This patient has an **elevated serum TSH** and **decreased thyroxine (T4) level**, findings consistent with **primary hypothyroidism**. The most common congenital causes are thyroid dysgenesis (eg, ectopy, hypoplasia) and TSH resistance. Less common, transient etiologies are usually due to maternal conditions (eg, iodine excess, antithyroid medications). Given that this patient's **thyroid is normal in size and location** and the mother has no medical conditions, the most likely cause is thyroid gland resistance to TSH.

TSH is normally produced by the anterior pituitary and binds to TSH receptors on follicular thyroid cells to stimulate T4 production. In TSH resistance, a **mutation in the TSH receptor gene** leads to thyroid insensitivity to TSH and reduced synthesis of T4. Low T4 leads to positive feedback to the pituitary, further increasing TSH levels.

Newborns are usually asymptomatic due to placentally transferred maternal T4 (although thyroid hormones do not readily cross the placenta, enough T4 can usually cross to prevent development of overt symptoms); diagnosis is typically via newborn screening. Treatment is lifelong levothyroxine.

(Choice A) Central hypothyroidism (eg, panhypopituitarism) causes low serum T4 due to decreased production of TSH by the anterior pituitary. This patient's elevated TSH is inconsistent with central hypothyroidism.

(Choice B) Generalized resistance to thyroid hormones due to a thyroid hormone–receptor mutation may lead to hypothyroidism due to insensitivity to T4. However, this condition causes elevated T4 and TSH.

(Choice D) Thyroid hormone–binding globulin deficiency is a benign, euthyroid state characterized by a low total T4 but normal free T4 and TSH levels.

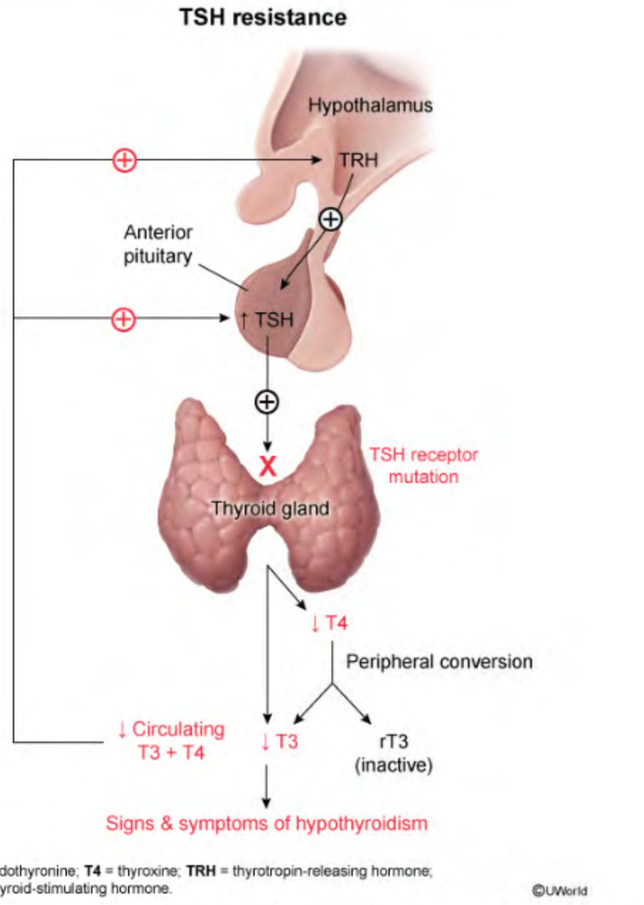
(Choice E) Transplacental transfer of TSH receptor–stimulating antibodies in a mother with Graves disease can cause transient neonatal hyperthyroidism (neonatal Graves disease). Neonatal symptoms include tachycardia and irritability, and laboratory evaluation would show high T4 and low TSH.

Educational objective:
TSH resistance due to a mutation in the TSH receptor gene presents with congenital hypothyroidism, which is characterized by increased TSH and low thyroxine. The thyroid gland is normal in size and location.

https://t.me/USMLEWorldStep1

- Antithyroid medications

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

This p
hypot
resista
antithy
medic

TSH is
T4 pro
reduce

Newbo
readily
typical

(Choi
TSH b

(Choi
hypoth

(Choi
T4 but

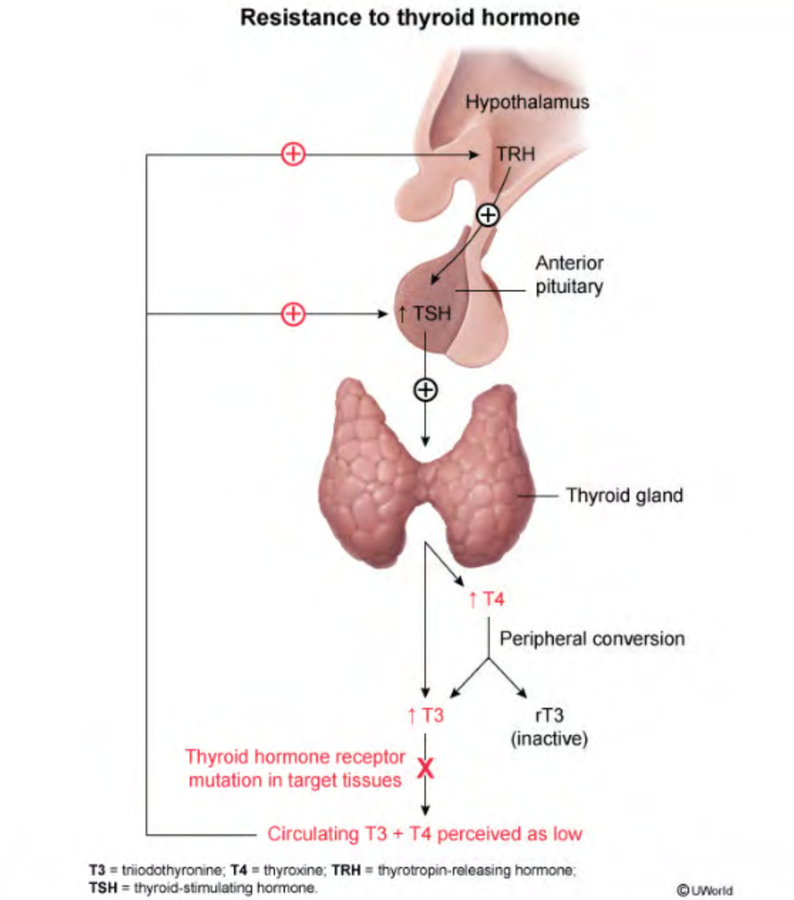
(Choi
cause
irritabi

Educa
TSH re
characterized by increased TSH and low thyroxine. The thyroid gland is normal in size and location.

https://t.me/USMLEWorldStep1

- Antithyroid medications

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

This p
hypot
resista
antithy
medic

TSH is
T4 pro
reduce

Newbo
readily
typical

(Choi
TSH b

(Choi
hypoth

(Choi
T4 but

(Choi
cause
irritabi

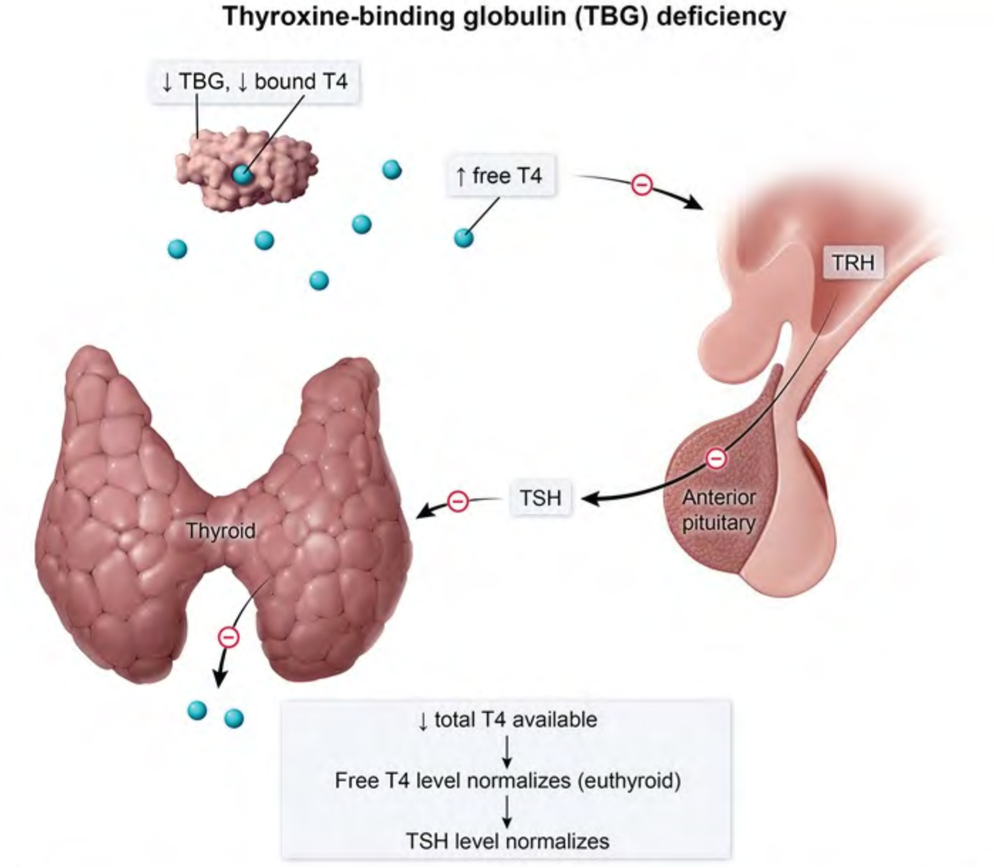
Educa
TSH re

characterized by increased TSH and low thyroxine. The thyroid gland is normal in size and location.

https://t.me/USMLEWorldStep1

- Antithyroid medications

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

This p
hypot
resista
antithy
medic

TSH is
T4 pro
reduce

Newbo
readily
typical

(Choi
TSH b

(Choi
hypoth

(Choi
T4 but

(Choi
cause
irritabi

Educa
TSH re

characterized by increased TSH and low thyroxine. The thyroid gland is normal in size and location.

https://t.me/USMLEWorldStep1

A 4-week-old infant is evaluated for frequent episodes of hypoglycemia. The patient is found to have elevated insulin levels during periods of fasting. Several members of his family have a similar condition. Genetic testing reveals a mutation involving potassium channels expressed in pancreatic beta cells. The mutated channels have a higher sensitivity to the substance that normally modulates their activity, causing increased beta cell secretory activity. Which of the following substances normally binds to and regulates the ion channels that are responsible for this patient's hypoglycemia?

- A. ATP
- B. Citrate
- C. Fructose-6-phosphate
- D. Fumarate
- E. Glucose
- F. Lactate
- G. Malate
- H. Pyruvate

Submit

https://t.me/USMLEWorldStep1

A 4-week-old infant is evaluated for frequent episodes of hypoglycemia. The patient is found to have elevated insulin levels during periods of fasting. Several members of his family have a similar condition. Genetic testing reveals a mutation involving potassium channels expressed in pancreatic beta cells. The mutated channels have a higher sensitivity to the substance that normally modulates their activity, causing increased beta cell secretory activity. Which of the following substances normally binds to and regulates the ion channels that are responsible for this patient's hypoglycemia?

- ✓ A. ATP (68%)
- B. Citrate (2%)
- ✗ C. Fructose-6-phosphate (3%)
- D. Fumarate (0%)
- E. Glucose (22%)
- F. Lactate (0%)
- G. Malate (0%)
- H. Pyruvate (1%)

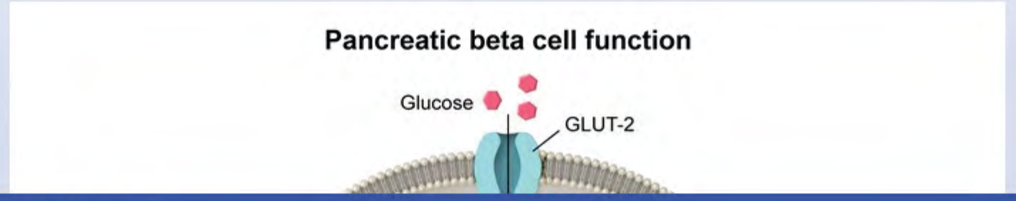
Incorrect
Correct answer
A

68%
Answered correctly

04 secs
Time Spent

2023
Version

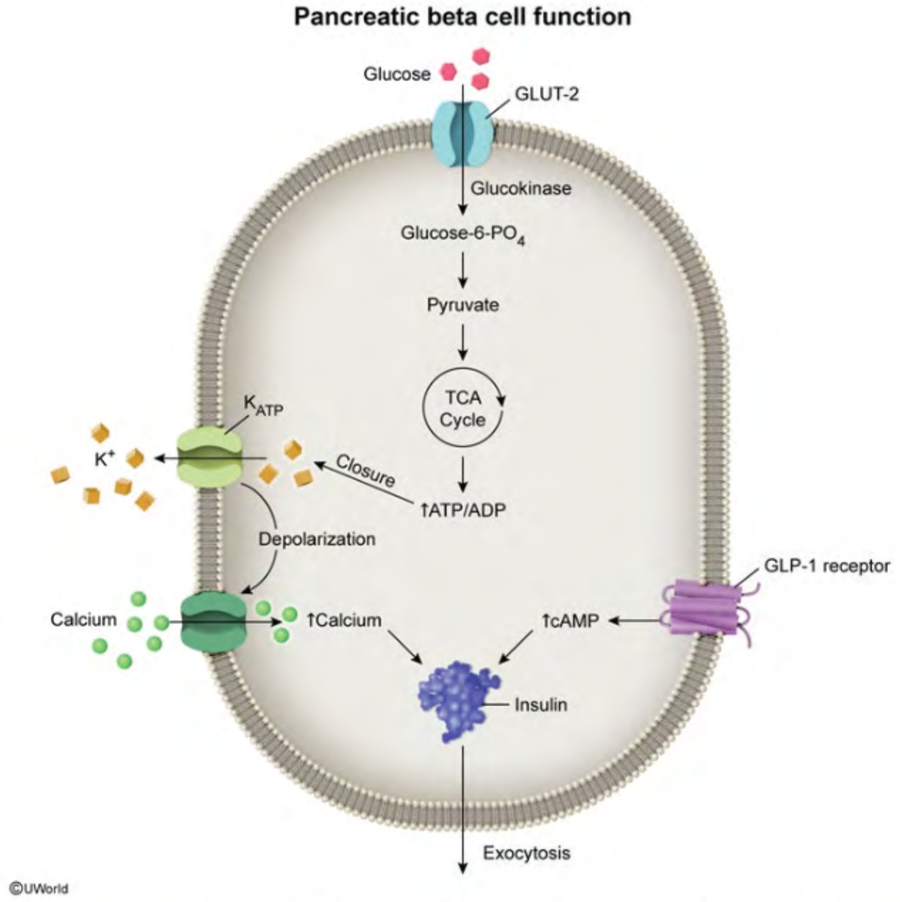
Explanation



https://t.me/USMLEWorldStep1

A 4-week-old infant is evaluated for frequent episodes of hypoglycemia. The patient is found to have elevated insulin reveal higher activity for this

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Incc
Corre
A

Expl

https://t.me/USMLEWorldStep1

©UWorld

Pancreatic beta cells secrete insulin in response to elevated **glucose** levels. Glucose enters beta cells via **glucose transporter 2** (GLUT-2) and is metabolized via glycolysis and the citric acid cycle to generate **ATP**. ATP then binds to the regulatory subunit of the **ATP-sensitive potassium channel** (K_{ATP} channel). K_{ATP} channels are normally open at rest and maintain membrane polarization by allowing outward movement of potassium from the beta cells; however, on binding ATP, the K_{ATP} channels close. Increased intracellular ATP therefore leads to decreased potassium efflux and **membrane depolarization**. This triggers opening of voltage-dependent calcium channels, increased intracellular calcium levels, and subsequent **insulin release**.

Mutations in the K_{ATP} channel causing increased affinity for ATP result in fewer open channels and depolarization at lower glucose concentrations. This causes continued secretion of insulin despite falling blood glucose levels, leading to congenital hypoglycemia. Conversely, mutations of the K_{ATP} channels that decrease ATP affinity prevent appropriate depolarization in response to rising glucose levels, causing a familial form of neonatal diabetes mellitus. These patients can be treated successfully with sulfonylureas, which bind to K_{ATP} channels and cause closure independent of ATP.

(Choices B, D, and G) Citrate, fumarate, and malate are intermediate products in the citric acid cycle. During this process, energy is stored as NADH and $FADH_2$. ATP is then produced when NADH and $FADH_2$ enter oxidative phosphorylation. However, these intermediates do not directly interact with K_{ATP} channels.

(Choices C, F, and H) Fructose-6-phosphate and pyruvate are products of the glycolytic pathway. Lactate is produced from pyruvate during anaerobic glycolysis. Glycolysis raises intracellular ATP levels, but these glycolytic intermediates do not act on K_{ATP} channels directly.

(Choice E) Glucose induces insulin release from beta cells via ATP formation but does not interact with K_{ATP} channels directly.

Educational objective:
Oxidative metabolism of glucose in pancreatic beta cells generates ATP. ATP-induced closure of the ATP-sensitive potassium channels leads to membrane depolarization and subsequent insulin release.

References

https://t.me/USMLEWorldStep1

A 65-year-old man comes to the physician because of a non-healing ulcer on his right foot. His past medical history is significant for recurrent high blood glucose readings for the last several years, because he has failed to comply with appropriate treatment. His BMI is 37 kg/m^2. Physical examination is significant for a bilateral symmetric decrease in vibration sensation over the feet and ankles. Which of the following is most likely to be associated with this patient's condition?

- A. Pancreatic islet infiltration with leukocytes
- B. Pancreatic islet amyloid deposition
- C. Circulating anti-islet antibodies
- D. Strong linkage with HLA class II gene makeup
- E. Episodic ketoacidosis that requires insulin therapy

Submit

https://t.me/USMLEWorldStep1

A 65-year-old man comes to the physician because of a non-healing ulcer on his right foot. His past medical history is significant for recurrent high blood glucose readings for the last several years, because he has failed to comply with appropriate treatment. His BMI is 37 kg/m^2. Physical examination is significant for a bilateral symmetric decrease in vibration sensation over the feet and ankles. Which of the following is most likely to be associated with this patient's condition?

- ✗ A. Pancreatic islet infiltration with leukocytes (4%)
- ✓ B. Pancreatic islet amyloid deposition (67%)
- C. Circulating anti-islet antibodies (3%)
- D. Strong linkage with HLA class II gene makeup (16%)
- E. Episodic ketoacidosis that requires insulin therapy (7%)

Incorrect
Correct answer
B

67%
Answered correctly

04 secs
Time Spent

2023
Version

Explanation

The patient described in this vignette has type 2 diabetes mellitus (advanced age, obesity, prolonged non-compliance with treatment without immediate life-threatening consequences). The two cardinal defects involved in the pathophysiology of type 2 diabetes mellitus are increased insulin resistance and defective insulin secretion. Although still controversial, many researchers believe that increased insulin resistance is the primary abnormality in type 2 diabetes mellitus. Early in the pathogenesis of type 2 diabetes, glucose tolerance is thought to remain normal because of a compensatory increase in insulin secretion from beta cells. This compensatory insulin response by beta cells ultimately fails, causing poor glucose tolerance. A number of genetic and acquired factors are implicated in the beta-cell dysregulation of type 2 diabetes. Islet amyloid polypeptide (amylin) is one factor thought to be responsible for this beta cell dysfunction. Amylin is stored in insulin secretory granules and is co-secreted with insulin from pancreatic beta cells. Deposits of amylin are universally seen in the pancreatic islets of

https://t.me/USMLEWorldStep1

Explanation

The patient described in this vignette has type 2 diabetes mellitus (advanced age, obesity, prolonged non-compliance with treatment without immediate life-threatening consequences). The two cardinal defects involved in the pathophysiology of type 2 diabetes mellitus are increased insulin resistance and defective insulin secretion. Although still controversial, many researchers believe that increased insulin resistance is the primary abnormality in type 2 diabetes mellitus. Early in the pathogenesis of type 2 diabetes, glucose tolerance is thought to remain normal because of a compensatory increase in insulin secretion from beta cells. This compensatory insulin response by beta cells ultimately fails, causing poor glucose tolerance. A number of genetic and acquired factors are implicated in the beta-cell dysregulation of type 2 diabetes. Islet amyloid polypeptide (amylin) is one factor thought to be responsible for this beta cell dysfunction. Amylin is stored in insulin secretory granules and is co-secreted with insulin from pancreatic beta cells. Deposits of amylin are universally seen in the pancreatic islets of patients with type 2 diabetes mellitus. Amylin may play a causative role in beta cell apoptosis and defective insulin secretion; however, this theory is still controversial.

Type 1 and type 2 diabetes mellitus have very strong genetic components. Twin studies have shown a concordance rate of 50% in identical twins for diabetes mellitus type 1, and around 80% for diabetes mellitus type 2. The genes involved in the pathogenesis of diabetes mellitus type 2 remain largely unknown. Gene polymorphism within the major histocompatibility complex contributes to type 1 diabetes mellitus disease in humans. HLA-DQ and -DR are the most important determinants of type 1 diabetes mellitus. In the general population, DR3 and DR4 are seen in approximately 40% of subjects; however, in patients with type 1 diabetes mellitus, DR3 and DR4 haplotypes are seen in more than 90% of subjects.

(Choices A, C, D & E) These are features of type 1 diabetes mellitus. Type 1 diabetes occurs when an autoimmune response is triggered by an environmental insult in genetically susceptible individuals. Patients with type 2 diabetes retain at least some beta cell function, but patients with type 1 diabetes mellitus develop absolute deficiency of insulin secondary to immune destruction of pancreatic beta cells. These patients need insulin for survival. Discontinuation of insulin treatment results in ketoacidosis.

Educational objective:

https://t.me/USMLEWorldStep1

compliance with treatment without immediate life-threatening consequences). The two cardinal defects involved in the pathophysiology of type 2 diabetes mellitus are increased insulin resistance and defective insulin secretion. Although still controversial, many researchers believe that increased insulin resistance is the primary abnormality in type 2 diabetes mellitus. Early in the pathogenesis of type 2 diabetes, glucose tolerance is thought to remain normal because of a compensatory increase in insulin secretion from beta cells. This compensatory insulin response by beta cells ultimately fails, causing poor glucose tolerance. A number of genetic and acquired factors are implicated in the beta-cell dysregulation of type 2 diabetes. Islet amyloid polypeptide (amylin) is one factor thought to be responsible for this beta cell dysfunction. Amylin is stored in insulin secretory granules and is co-secreted with insulin from pancreatic beta cells. Deposits of amylin are universally seen in the pancreatic islets of patients with type 2 diabetes mellitus. Amylin may play a causative role in beta cell apoptosis and defective insulin secretion; however, this theory is still controversial.

Type 1 and type 2 diabetes mellitus have very strong genetic components. Twin studies have shown a concordance rate of 50% in identical twins for diabetes mellitus type 1, and around 80% for diabetes mellitus type 2. The genes involved in the pathogenesis of diabetes mellitus type 2 remain largely unknown. Gene polymorphism within the major histocompatibility complex contributes to type 1 diabetes mellitus disease in humans. HLA-DQ and -DR are the most important determinants of type 1 diabetes mellitus. In the general population, DR3 and DR4 are seen in approximately 40% of subjects; however, in patients with type 1 diabetes mellitus, DR3 and DR4 haplotypes are seen in more than 90% of subjects.

(Choices A, C, D & E) These are features of type 1 diabetes mellitus. Type 1 diabetes occurs when an autoimmune response is triggered by an environmental insult in genetically susceptible individuals. Patients with type 2 diabetes retain at least some beta cell function, but patients with type 1 diabetes mellitus develop absolute deficiency of insulin secondary to immune destruction of pancreatic beta cells. These patients need insulin for survival. Discontinuation of insulin treatment results in ketoacidosis.

Educational objective:
Pancreatic islet amyloid deposition is characteristic of type 2 diabetes mellitus. A strong linkage with HLA class II gene makeup, pancreatic islet infiltration with leukocytes (insulitis), and antibodies against islet antigens are frequently seen in type 1 diabetes.

https://t.me/USMLEWorldStep1

A 79-year-old man comes to the office for routine follow-up for chronic conditions. The patient has hypertension, for which he takes amlodipine, and mild Alzheimer dementia, which is managed by his family with behavioral measures. Medical history is notable for locally advanced prostate cancer, for which chronic leuprolide therapy has been prescribed. The patient is otherwise healthy, eats a balanced diet, and exercises regularly. Bone density testing with DXA was normal 2 years ago but now reveals osteoporosis. Which of the following is the most likely cause of the reduced bone density in this patient?

- A. Decreased estrogen and testosterone levels
- B. Decreased intestinal calcium absorption
- C. Impaired 25-hydroxycholecalciferol activation
- D. Increased parathyroid hormone levels
- E. Paraneoplastic effects of the cancer cells

Submit

https://t.me/USMLEWorldStep1

A 79-year-old man comes to the office for routine follow-up for chronic conditions. The patient has hypertension, for which he takes amlodipine, and mild Alzheimer dementia, which is managed by his family with behavioral measures. Medical history is notable for locally advanced prostate cancer, for which chronic leuprolide therapy has been prescribed. The patient is otherwise healthy, eats a balanced diet, and exercises regularly. Bone density testing with DXA was normal 2 years ago but now reveals osteoporosis. Which of the following is the most likely cause of the reduced bone density in this patient?

- ✓ A. Decreased estrogen and testosterone levels
- ✗ B. Decreased intestinal calcium absorption
- C. Impaired 25-hydroxycholecalciferol activation
- D. Increased parathyroid hormone levels
- E. Paraneoplastic effects of the cancer cells

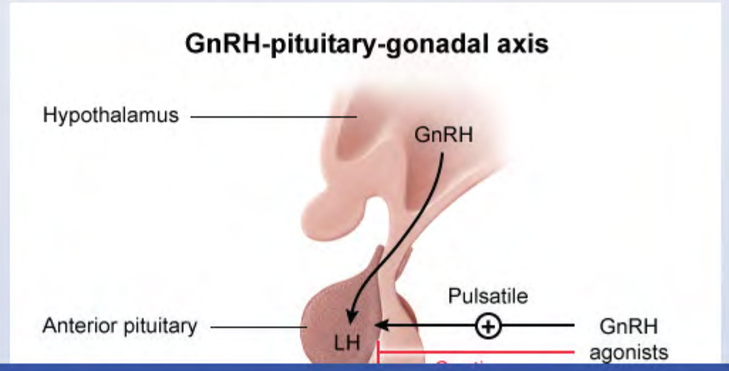
Incorrect
Correct answer
A

Collecting Statistics

04 secs
Time Spent

2023
Version

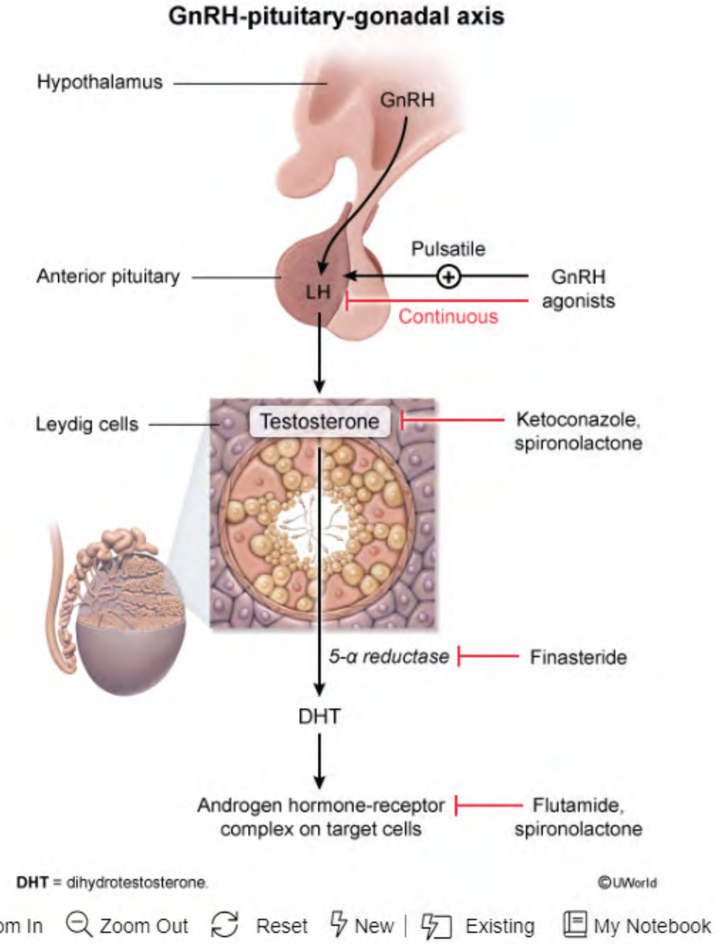
Explanation



https://t.me/USMLEWorldStep1

A. Decreased estrogen and testosterone levels

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

Leuprolide is a GnRH analogue used in the treatment of prostate cancer to suppress testosterone levels. When administered in a pulsatile fashion (eg, intermittent intravenous infusion), leuprolide has GnRH agonist properties; however, **chronic administration** (eg, depot injection) results in a continuous GnRH effect that leads to downregulation of GnRH receptors on gonadotropin cells in the pituitary gland. This suppresses pituitary LH release and leads to **reduced** production of **testosterone** by Leydig cells. Lower levels of circulating testosterone produce a clinical effect similar to that of surgical orchiectomy.

In male patients, androgens (eg, testosterone) are **aromatized to estrogens** that preserve bone density by reducing expression of receptor activator of nuclear factor kappa-B (RANK) on osteoclast precursors and inducing production of osteoprotegerin (decoy receptor that opposes RANK-ligand) by osteoblasts. The net effect is to prolong survival of osteoblasts, reduce differentiation and survival of osteoclasts, and decrease bone turnover. Leuprolide therapy reduces testosterone and subsequent estrogen production and can lead to **accelerated bone loss** and increased risk for **osteoporosis**.

(Choice B) Glucocorticoids (eg, prednisone) and proton pump inhibitors (eg, omeprazole) are associated with an increased risk for osteoporosis, at least partly due to the decreased intestinal absorption of calcium. GnRH analogues have little effect on intestinal calcium absorption.

(Choices C and D) Elevated parathyroid hormone (PTH) levels stimulate osteoclast activity and release of calcium from bone, increasing osteoporosis risk. Similarly, low vitamin D concentrations lead to impaired calcium absorption with a compensatory increase in PTH. Conversion of 25-hydroxyvitamin D (ie, 25-hydroxycholecalciferol) to its active form, 1,25-dihydroxyvitamin D, by 1-alpha-hydroxylase (stimulated by PTH) occurs in the kidneys; this is one reason that patients with chronic kidney disease are at increased risk for osteoporosis. However, the vitamin D–PTH axis is not significantly influenced by leuprolide.

(Choice E) Humoral hypercalcemia of malignancy (HHM) is a paraneoplastic syndrome due to release of PTH-related protein (PTHrP) by malignant cells. PTHrP is structurally similar to PTH and acts on the PTH-1 receptor. HHM is most commonly seen in squamous cell carcinoma (eg, lung), transitional cell carcinomas, and breast and ovarian cancers. It typically presents with severe, symptomatic hypercalcemia (eg, constipation, lethargy) rather than osteoporosis.

Educational objective:

https://t.me/USMLEWorldStep1

In male patients, androgens (eg, testosterone) are **aromatized to estrogens** that preserve bone density by reducing expression of receptor activator of nuclear factor kappa-B (RANK) on osteoclast precursors and inducing production of osteoprotegerin (decoy receptor that opposes RANK-ligand) by osteoblasts. The net effect is to prolong survival of osteoblasts, reduce differentiation and survival of osteoclasts, and decrease bone turnover. Leuprolide therapy reduces testosterone and subsequent estrogen production and can lead to **accelerated bone loss** and increased risk for **osteoporosis**.

(Choice B) Glucocorticoids (eg, prednisone) and proton pump inhibitors (eg, omeprazole) are associated with an increased risk for osteoporosis, at least partly due to the decreased intestinal absorption of calcium. GnRH analogues have little effect on intestinal calcium absorption.

(Choices C and D) Elevated parathyroid hormone (PTH) levels stimulate osteoclast activity and release of calcium from bone, increasing osteoporosis risk. Similarly, low vitamin D concentrations lead to impaired calcium absorption with a compensatory increase in PTH. Conversion of 25-hydroxyvitamin D (ie, 25-hydroxycholecalciferol) to its active form, 1,25-dihydroxyvitamin D, by 1-alpha-hydroxylase (stimulated by PTH) occurs in the kidneys; this is one reason that patients with chronic kidney disease are at increased risk for osteoporosis. However, the vitamin D–PTH axis is not significantly influenced by leuprolide.

(Choice E) Humoral hypercalcemia of malignancy (HHM) is a paraneoplastic syndrome due to release of PTH-related protein (PTHrP) by malignant cells. PTHrP is structurally similar to PTH and acts on the PTH-1 receptor. HHM is most commonly seen in squamous cell carcinoma (eg, lung), transitional cell carcinomas, and breast and ovarian cancers. It typically presents with severe, symptomatic hypercalcemia (eg, constipation, lethargy) rather than osteoporosis.

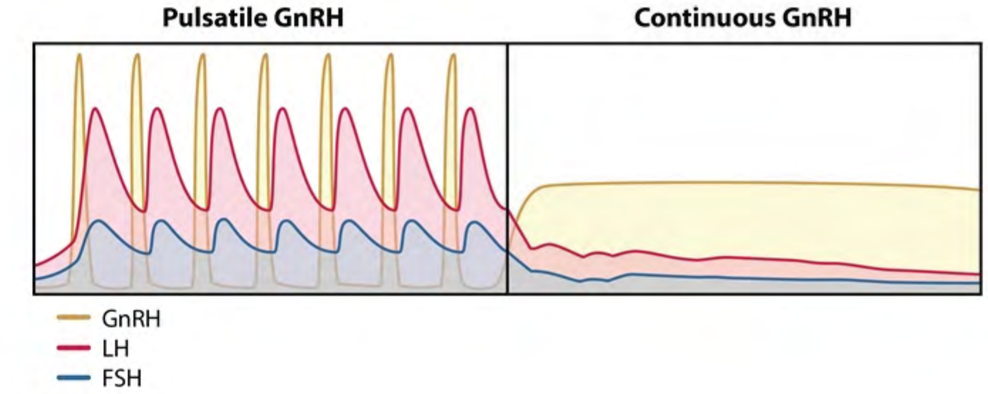
Educational objective:
Chronic administration of GnRH agonists (eg, leuprolide) suppresses pituitary LH release and leads to reduced production of testosterone. Lower levels of circulating testosterone produce a clinical effect similar to that of surgical orchiectomy and can lead to accelerated bone loss and increased risk for osteoporosis.

Pharmacology	Endocrine, Diabetes & Metabolism	Osteoporosis
Subject	System	Topic

https://t.me/USMLEWorldStep1

Androgen hormone-receptor — Flutamide,

Exhibit Display



©UWorld

Zoom In Zoom Out Reset New | Existing My Notebook

Leupr
admin
howev
downr
releas
produc

In mal
reduci
produc
prolon
Leupr
loss a

(Choi
increa
analog

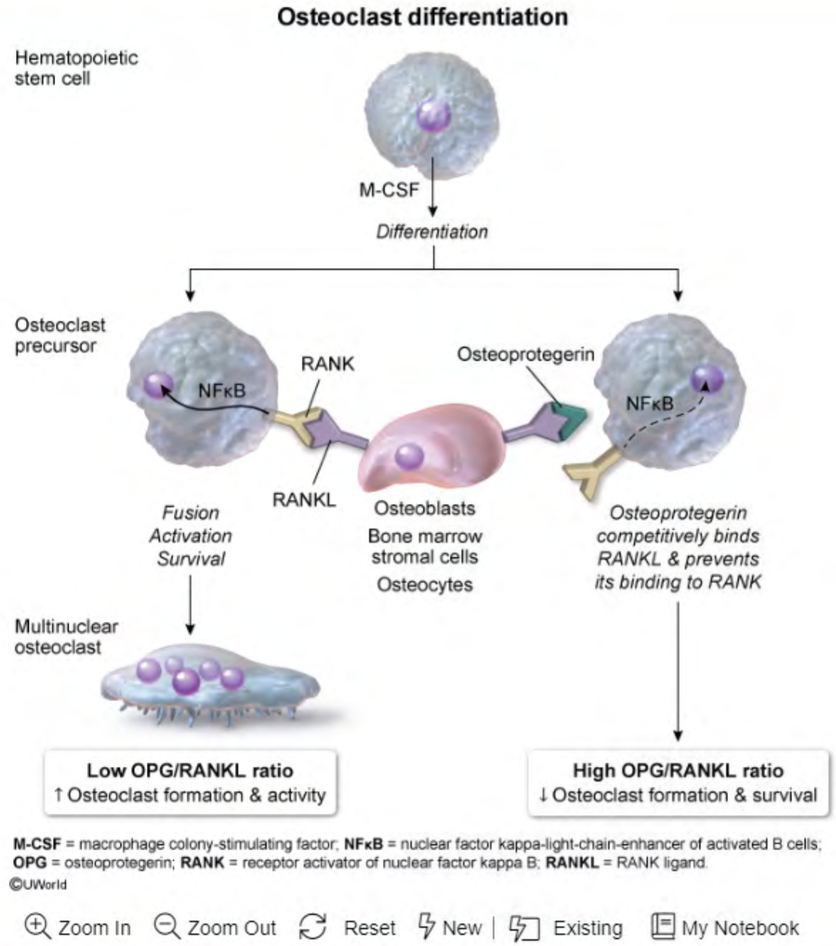
(Choi
calciu
absorp
hydrox
occurs
osteop

(Choi
related protein (PTHrP) by malignant cells. PTHrP is structurally similar to PTH and acts on the PTH-1 receptor.
HHM is most commonly seen in squamous cell carcinoma (eg, lung), transitional cell carcinomas, and breast and

https://t.me/USMLEWorldStep1

Androgen hormone-receptor — Flutamide,

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Leupr
admin
howev
downr
releas
produc

In mal
reduci
produc
prolon
Leupr
loss a

(Choi
increa
analog

(Choi
calciu
absorp
hydrox
occurs
osteop

(Choi
related protein (PTHrP) by malignant cells. PTHrP is structurally similar to PTH and acts on the PTH-1 receptor.
HHM is most commonly seen in squamous cell carcinoma (eg, lung), transitional cell carcinomas, and breast and

https://t.me/USMLEWorldStep1

A 34-year-old man is admitted to the hospital after sustaining a head injury and fractures of both femurs in a motor vehicle collision. CT scan of the head reveals a left-sided extradural hematoma. He has no history of chronic illness and takes no medications. The patient receives intravenous fluid boluses and blood transfusions and is taken to the operating room for fracture repair and removal of the hematoma. On the first postoperative day, laboratory results show high plasma glucose and lactate levels. Which of the following is the primary contributor to this patient's elevated blood glucose levels?

- A. Administration of intravenous fluid boluses
- B. Decreased hepatic glycerol supply
- C. Increased anaerobic glycolysis
- D. Increased hepatic glucose production
- E. Increased renal gluconeogenesis

Submit

https://t.me/USMLEWorldStep1

A 34-year-old man is admitted to the hospital after sustaining a head injury and fractures of both femurs in a motor vehicle collision. CT scan of the head reveals a left-sided extradural hematoma. He has no history of chronic illness and takes no medications. The patient receives intravenous fluid boluses and blood transfusions and is taken to the operating room for fracture repair and removal of the hematoma. On the first postoperative day, laboratory results show high plasma glucose and lactate levels. Which of the following is the primary contributor to this patient's elevated blood glucose levels?

- ✗ A. Administration of intravenous fluid boluses (9%)
- B. Decreased hepatic glycerol supply (2%)
- C. Increased anaerobic glycolysis (19%)
- ✓ D. Increased hepatic glucose production (64%)
- E. Increased renal gluconeogenesis (4%)

Incorrect
Correct answer
D

64%
Answered correctly

04 secs
Time Spent

2023
Version

Explanation

Stress hyperglycemia	
Presentation	• Transient hyperglycemia without known diabetes
Risk factors	• Hemorrhage, major trauma • Hypoxia • Sepsis
Pathogenesis	• Secretion of cortisol, catecholamines, glucagon & proinflammatory cytokines • Increased hepatic glycogenolysis & gluconeogenesis

https://t.me/USMLEWorldStep1

Stress hyperglycemia	
Presentation	• Transient hyperglycemia without known diabetes
Risk factors	• Hemorrhage, major trauma • Hypoxia • Sepsis
Pathogenesis	• Secretion of cortisol, catecholamines, glucagon & proinflammatory cytokines • Increased hepatic glycogenolysis & gluconeogenesis

Stress hyperglycemia is a transiently elevated blood glucose level in the context of severe illness in patients without preexisting diabetes mellitus. It is common in the intensive care unit and is typically seen in those with sepsis and other severe infections, burns, trauma, or major hemorrhage.

Severe metabolic stress is associated with increased production of **cortisol**, **catecholamines** (primarily epinephrine and norepinephrine), glucagon, and proinflammatory cytokines (eg, IL-1, IL-6, tumor necrosis factor-alpha). Cortisol, catecholamines, and glucagon act on the liver to **increase glycogenolysis and gluconeogenesis**, stimulating release of glucose from the liver into the blood.

In addition, the release of proinflammatory cytokines is associated with increased expression of glucose transporter (GLUT) 1 in the CNS and macrophages, along with decreased expression of GLUT4 (which mediates insulin-induced glucose uptake in peripheral tissues). This facilitates **increased glucose uptake by the brain** and **immune cells** responsible for fighting infection.

(Choice A) During trauma resuscitation, most patients are given isotonic fluids (eg, normal saline, Ringer lactate), which are unlikely to cause hyperglycemia. Even if mild fluid-induced hyperglycemia occurs, blood glucose levels typically normalize quickly after fluid boluses.

(Choice B) Norepinephrine stimulates peripheral lipolysis, releasing glycerol, which can be taken up by the liver for use in gluconeogenesis. Therefore, stress increases, not decreases, the hepatic glycerol supply.

(Choice C) Severe illness is often associated with increased anaerobic glycolysis due to systemic or local tissue hypoxia (blood loss in this patient). Increased conversion of glucose to lactate in ischemic tissues *raises plasma*

https://t.me/USMLEWorldStep1

without preexisting diabetes mellitus. It is common in the intensive care unit and is typically seen in those with sepsis and other severe infections, burns, trauma, or major hemorrhage.

Severe metabolic stress is associated with increased production of **cortisol**, **catecholamines** (primarily epinephrine and norepinephrine), glucagon, and proinflammatory cytokines (eg, IL-1, IL-6, tumor necrosis factor-alpha). Cortisol, catecholamines, and glucagon act on the liver to **increase glycogenolysis and gluconeogenesis**, stimulating release of glucose from the liver into the blood.

In addition, the release of proinflammatory cytokines is associated with increased expression of glucose transporter (GLUT) 1 in the CNS and macrophages, along with decreased expression of GLUT4 (which mediates insulin-induced glucose uptake in peripheral tissues). This facilitates **increased glucose uptake by the brain** and **immune cells** responsible for fighting infection.

(Choice A) During trauma resuscitation, most patients are given isotonic fluids (eg, normal saline, Ringer lactate), which are unlikely to cause hyperglycemia. Even if mild fluid-induced hyperglycemia occurs, blood glucose levels typically normalize quickly after fluid boluses.

(Choice B) Norepinephrine stimulates peripheral lipolysis, releasing glycerol, which can be taken up by the liver for use in gluconeogenesis. Therefore, stress increases, not decreases, the hepatic glycerol supply.

(Choice C) Severe illness is often associated with increased anaerobic glycolysis due to systemic or local tissue hypoxia (blood loss in this patient). Increased conversion of glucose to lactate in ischemic tissues *raises plasma lactate levels*. Glucose levels are often concurrently elevated due to stress hyperglycemia, but anaerobic glycolysis itself depletes glucose.

(Choice E) The renal cortex can convert lactate to glucose via gluconeogenesis. However, it makes a significantly smaller contribution to circulating glucose levels than hepatic gluconeogenesis.

Educational objective:
Stress hyperglycemia is transiently elevated blood glucose levels in the context of severe illness (eg, sepsis, burns, major hemorrhage) in patients without preexisting diabetes mellitus. Cortisol and catecholamines released in response to severe metabolic stress act on the liver to increase glycogenolysis and gluconeogenesis.

References

https://t.me/USMLEWorldStep1

A 46-year-old woman comes to the office with a painful rash involving her groin and legs that has been worsening over the last 2 weeks. She was diagnosed with diabetes mellitus 6 months ago but has no other medical problems other than occasional loose stools. Physical examination shows coalescing erythematous plaques with crusting and scaling at the borders and central areas of brownish induration. Biopsy of the lesions reveals superficial necrolysis. Which of the following laboratory abnormalities is most likely to be present in this patient?

- A. Elevated amino acids
- B. Elevated gastrin
- C. Elevated glucagon
- D. Elevated somatostatin
- E. Elevated vasoactive intestinal polypeptide
- F. Low insulin
- G. Low zinc

Submit

https://t.me/USMLEWorldStep1

A 46-year-old woman comes to the office with a painful rash involving her groin and legs that has been worsening over the last 2 weeks. She was diagnosed with diabetes mellitus 6 months ago but has no other medical problems other than occasional loose stools. Physical examination shows coalescing erythematous plaques with crusting and scaling at the borders and central areas of brownish induration. Biopsy of the lesions reveals superficial necrolysis. Which of the following laboratory abnormalities is most likely to be present in this patient?

- A. Elevated amino acids (3%)
- ✗ B. Elevated gastrin (2%)
- ✓ C. Elevated glucagon (30%)
- D. Elevated somatostatin (4%)
- E. Elevated vasoactive intestinal polypeptide (9%)
- F. Low insulin (10%)
- G. Low zinc (38%)

Incorrect
Correct answer
C

30%
Answered correctly

05 secs
Time Spent

2023
Version

Explanation

Features of glucagonoma	
Clinical presentation	• **Necrolytic migratory erythema** • Erythematous papules/plaques on face, perineum & extremities • Lesions enlarge & coalesce, leaving a central indurated area with peripheral blistering & scaling • **Diabetes mellitus**/hyperglycemia

https://t.me/USMLEWorldStep1

Features of glucagonoma	
Clinical presentation	• **Necrolytic migratory erythema** • Erythematous papules/plaques on face, perineum & extremities • Lesions enlarge & coalesce, leaving a central indurated area with peripheral blistering & scaling • **Diabetes mellitus**/hyperglycemia • Gastrointestinal symptoms (diarrhea, anorexia, abdominal pain)
Diagnosis	• Markedly elevated glucagon levels

This patient most likely has a **glucagonoma**, a rare tumor arising from the **alpha cells** of the pancreatic islets of Langerhans. Glucagonomas secrete large quantities of glucagon, so affected patients often have **hyperglycemia** or overt **diabetes mellitus**. A characteristic skin finding is **necrolytic migratory erythema**, an elevated painful and pruritic rash typically affecting the face, groin, and extremities. Over time, small erythematous papules coalesce to form large, indurated plaques with a central clearing that often appears brown or bronze-colored. Diagnosis is made by detecting elevated levels of **glucagon** in the serum.

(Choice A) Glucagon acts on the liver to promote amino acid oxidation and gluconeogenesis from amino acids. Circulating levels of amino acids are low in glucagonoma and thought to contribute to development of necrolytic migratory erythema.

(Choice B) Elevated gastrin levels in patients with gastrinoma are associated with hypersecretion of gastric acid and resultant gastrointestinal ulceration. The peptic ulcers that occur with gastrinomas are often in unusual areas, such as the jejunum. Patients with gastrinomas can also have diarrhea and abdominal pain.

(Choice D) Excess somatostatin secretion from a somatostatinoma typically presents with abdominal pain, gallbladder stones, constipation, hyperglycemia, and steatorrhea. These manifestations result from somatostatin-induced inhibition of insulin, glucagon, gastrin, secretin, and cholecystokinin secretion, and inhibition of gastrointestinal motility.

(Choice E) High levels of vasoactive intestinal polypeptide (VIP) are seen in patients with a VIPoma, which

https://t.me/USMLEWorldStep1

(Choice A) Glucagon acts on the liver to promote amino acid oxidation and gluconeogenesis from amino acids. Circulating levels of amino acids are low in glucagonoma and thought to contribute to development of necrolytic migratory erythema.

(Choice B) Elevated gastrin levels in patients with gastrinoma are associated with hypersecretion of gastric acid and resultant gastrointestinal ulceration. The peptic ulcers that occur with gastrinomas are often in unusual areas, such as the jejunum. Patients with gastrinomas can also have diarrhea and abdominal pain.

(Choice D) Excess somatostatin secretion from a somatostatinoma typically presents with abdominal pain, gallbladder stones, constipation, hyperglycemia, and steatorrhea. These manifestations result from somatostatin-induced inhibition of insulin, glucagon, gastrin, secretin, and cholecystokinin secretion, and inhibition of gastrointestinal motility.

(Choice E) High levels of vasoactive intestinal polypeptide (VIP) are seen in patients with a VIPoma, which typically presents with intractable diarrhea, hypokalemia, and achlorhydria. Patients are usually hypotensive due to dehydration and the vasodilatory effects of VIP.

(Choice F) Diabetes mellitus is present in the majority of patients with glucagonoma, most likely due to excessive hepatic glucose production. Insulin levels tend to be normal but can be elevated secondary to hyperglycemia and glucagon-induced stimulation of the pancreatic beta cells.

(Choice G) Zinc deficiency causes erythematous skin lesions (mainly around body orifices) that are predominantly vesicular and pustular. Other features include hypogonadism, impaired taste and smell, night blindness, and impaired wound healing. Although the skin lesions in zinc deficiency can resemble necrolytic migratory erythema, this patient's lack of additional findings and her recent diabetes mellitus diagnosis make glucagonoma more likely.

Educational objective:
Glucagonoma presents with hyperglycemia (often as newly diagnosed diabetes mellitus) and necrolytic migratory erythema (blistering erythematous plaques with central clearing) affecting the groin, face, and extremities. The diagnosis is made by detecting elevated glucagon levels.

References

- The glucagonoma syndrome. Clinical and pathologic features in 21 patients.

https://t.me/USMLEWorldStep1

A 41-year-old man comes to the office due to a 4-month history of fatigue, headache, weight loss, sweating, and palpitations. He is otherwise healthy and takes no medications. He does not use tobacco, alcohol, or illicit drugs. Physical examination reveals lid lag and a fine hand tremor. Neck examination reveals mild, diffuse enlargement of the thyroid gland. Laboratory results are as follows:

TSH	10 µU/mL
Free thyroxine (T4)	3.0 ng/dL (normal: 0.9-1.7)
Total triiodothyronine (T3)	400 ng/dL

Which of the following is the most likely cause of this patient's disorder?

- A. Elevated thyroxine-binding globulin
- B. Graves disease
- C. Painless thyroiditis
- D. Pituitary tumor
- E. Thyroid cancer

Submit

https://t.me/USMLEWorldStep1

A 41-year-old man comes to the office due to a 4-month history of fatigue, headache, weight loss, sweating, and palpitations. He is otherwise healthy and takes no medications. He does not use tobacco, alcohol, or illicit drugs. Physical examination reveals lid lag and a fine hand tremor. Neck examination reveals mild, diffuse enlargement of the thyroid gland. Laboratory results are as follows:

TSH	10 µU/mL
Free thyroxine (T4)	3.0 ng/dL (normal: 0.9-1.7)
Total triiodothyronine (T3)	400 ng/dL

Which of the following is the most likely cause of this patient's disorder?

- ✗ A. Elevated thyroxine-binding globulin (4%)
- B. Graves disease (24%)
- C. Painless thyroiditis (3%)
- ✓ D. Pituitary tumor (64%)
- E. Thyroid cancer (3%)

Incorrect
Correct answer
D

64%
Answered correctly

04 secs
Time Spent

2023
Version

Explanation

Hypothalamic-pituitary-thyroid axis



https://t.me/USMLEWorldStep1

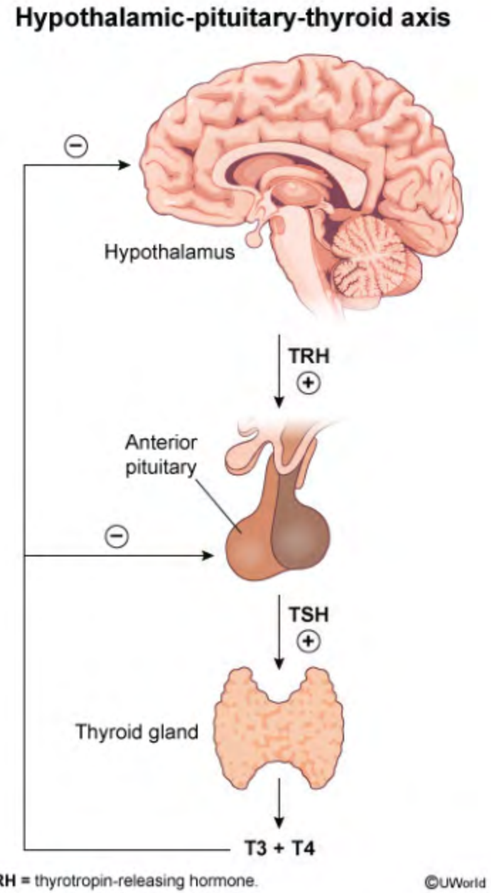
A 41-year-old man comes to the office due to a 4-month history of fatigue, headache, weight loss, sweating, and palpita
Physic
the thy

Which

Incc
Corre
D

Expl

Exhibit Display



Zoom In Zoom Out Reset New | Existing My Notebook

https://t.me/USMLEWorldStep1

The hypothalamus-pituitary-thyroid axis functions as follows:

- Thyroid hormone is released primarily as thyroxine (T4), with deiodination to triiodothyronine (T3) (the more active form) in peripheral tissues.
- Synthesis of thyroid hormone is driven by TSH secretion from the pituitary.
- TSH is regulated by thyrotropin-releasing hormone (TRH) from the hypothalamus.
- Secretion of both TRH and TSH is subject to negative feedback by T3.

Hyperthyroidism typically presents with fatigue, weight loss, and palpitations associated with elevated thyroid hormone levels. Hyperadrenergic signs (eg, lid lag, tremor) are also common. Most patients have primary hyperthyroidism (ie, intrinsic thyroid disorder with increased thyroid hormone release); TSH is low due to feedback suppression.

However, this patient has an **elevated TSH**, suggesting a pituitary etiology (ie, **secondary hyperthyroidism**). The most common cause of secondary hyperthyroidism is a TSH-secreting **pituitary adenoma**. The excess TSH causes generalized hypertrophy of the thyroid gland, manifesting as a **diffuse goiter**.

(Choice A) Most thyroid hormone is transported bound to plasma proteins, primarily thyroxine-binding globulin (TBG). Estrogen (eg, pregnancy, oral contraceptives) causes increased production of TBG, which lowers free thyroid hormone levels. A brief rise in TSH subsequently increases production of thyroid hormone to saturate the increased TBG binding sites, and the patient returns to a euthyroid state. Total T3 and T4 are elevated, but TSH and free hormone levels are normal.

(Choices B and C) Graves disease is caused by autoantibodies that activate the TSH receptor and induce thyroid hormone production. Painless thyroiditis is characterized by autoimmune destruction of thyroid follicles with release of preformed thyroid hormone. Both conditions cause hyperthyroidism with elevated thyroid hormone levels, but TSH is suppressed by feedback inhibition.

(Choice E) Thyroid cancer typically presents with a hard, asymmetric goiter. Adjacent thyroid tissue may be compressed and nonfunctional, but the contralateral lobe can usually compensate and patients are typically euthyroid. Thyroid follicular tumors may occasionally cause hyperthyroidism due to autonomous thyroid hormone production, but TSH is suppressed.

https://t.me/USMLEWorldStep1

- TSH is regulated by thyrotropin-releasing hormone (TRH) from the hypothalamus.
- Secretion of both TRH and TSH is subject to negative feedback by T3.

Hyperthyroidism typically presents with fatigue, weight loss, and palpitations associated with elevated thyroid hormone levels. Hyperadrenergic signs (eg, lid lag, tremor) are also common. Most patients have primary hyperthyroidism (ie, intrinsic thyroid disorder with increased thyroid hormone release); TSH is low due to feedback suppression.

However, this patient has an **elevated TSH**, suggesting a pituitary etiology (ie, **secondary hyperthyroidism**). The most common cause of secondary hyperthyroidism is a TSH-secreting **pituitary adenoma**. The excess TSH causes generalized hypertrophy of the thyroid gland, manifesting as a **diffuse goiter**.

(Choice A) Most thyroid hormone is transported bound to plasma proteins, primarily thyroxine-binding globulin (TBG). Estrogen (eg, pregnancy, oral contraceptives) causes increased production of TBG, which lowers free thyroid hormone levels. A brief rise in TSH subsequently increases production of thyroid hormone to saturate the increased TBG binding sites, and the patient returns to a euthyroid state. Total T3 and T4 are elevated, but TSH and free hormone levels are normal.

(Choices B and C) Graves disease is caused by autoantibodies that activate the TSH receptor and induce thyroid hormone production. Painless thyroiditis is characterized by autoimmune destruction of thyroid follicles with release of preformed thyroid hormone. Both conditions cause hyperthyroidism with elevated thyroid hormone levels, but TSH is suppressed by feedback inhibition.

(Choice E) Thyroid cancer typically presents with a hard, asymmetric goiter. Adjacent thyroid tissue may be compressed and nonfunctional, but the contralateral lobe can usually compensate and patients are typically euthyroid. Thyroid follicular tumors may occasionally cause hyperthyroidism due to autonomous thyroid hormone production, but TSH is suppressed.

Educational objective:
The most common cause of secondary hyperthyroidism is a TSH-secreting pituitary adenoma. In addition to hyperthyroid symptoms, TSH causes generalized hypertrophy of the thyroid gland (diffuse goiter). Laboratory evaluation shows elevated levels of thyroid hormone (triiodothyronine and thyroxine) and TSH.

https://t.me/USMLEWorldStep1

- TSH is regulated by thyrotropin-releasing hormone (TRH) from the hypothalamus.
- S[illegible]

Hyper
hormo
hypert
suppre

Howev
most c
cause

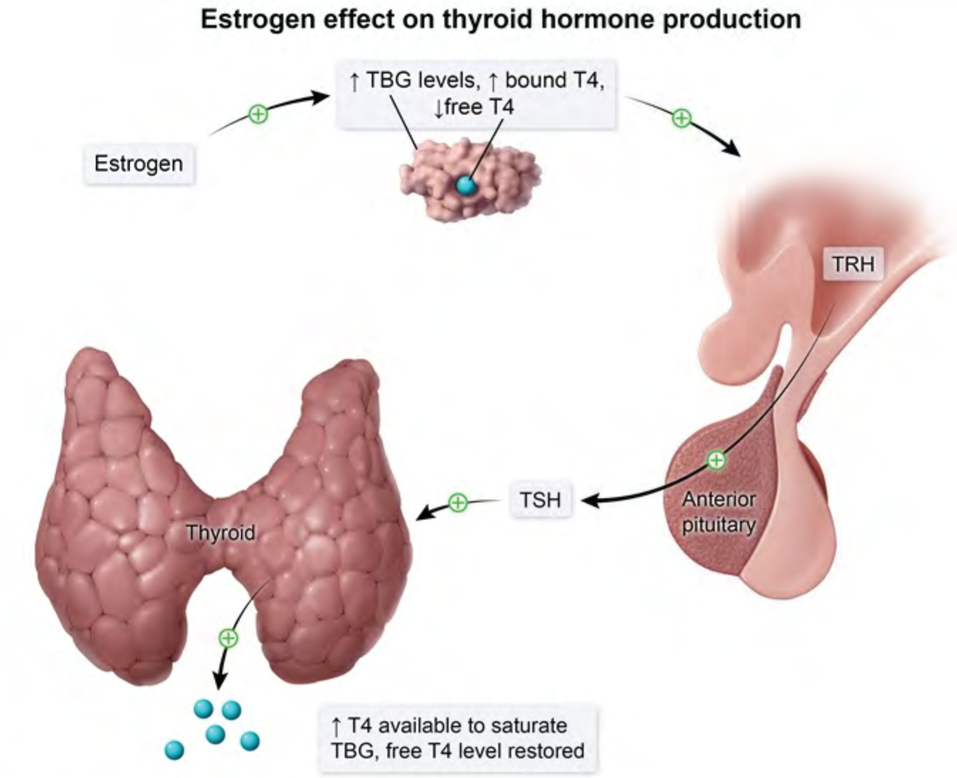
(Choi
(TBG)
thyroi
increa
and fre

(Choi
hormo
releas
levels,

(Choi
compr
euthyr
produc

Educa
The m
hypert
evaluation shows elevated levels of thyroid hormone (triiodothyronine and thyroxine) and TSH.

Exhibit Display



Zoom In Zoom Out Reset New | Existing My Notebook

https://t.me/USMLEWorldStep1

A 65-year-old woman comes to the clinic for a follow-up appointment. Medical history is notable for type 2 diabetes mellitus, hypertension, stable coronary artery disease, and heart failure with preserved ejection fraction. Blood pressure is 144/95 mm Hg. Physical examination shows no murmurs and the lungs are clear on auscultation. Fasting glucose is 122 mg/dL and hemoglobin A1c is 7.8%. The remainder of the laboratory results, including hepatic and renal markers, are within normal limits. She is prescribed canagliflozin. Which of the following potential complications should this patient be counseled on prior to initiation of this medication?

- A. Delayed gastric emptying
- B. Fluid overload
- C. Hypoglycemia
- D. Lactic acidosis
- E. Vaginitis
- F. Weight gain

Submit

https://t.me/USMLEWorldStep1

A 65-year-old woman comes to the clinic for a follow-up appointment. Medical history is notable for type 2 diabetes mellitus, hypertension, stable coronary artery disease, and heart failure with preserved ejection fraction. Blood pressure is 144/95 mm Hg. Physical examination shows no murmurs and the lungs are clear on auscultation. Fasting glucose is 122 mg/dL and hemoglobin A1c is 7.8%. The remainder of the laboratory results, including hepatic and renal markers, are within normal limits. She is prescribed canagliflozin. Which of the following potential complications should this patient be counseled on prior to initiation of this medication?

- A. Delayed gastric emptying (3%)
- ✗ B. Fluid overload (4%)
- C. Hypoglycemia (17%)
- D. Lactic acidosis (3%)
- ✓ E. Vaginitis (63%)
- F. Weight gain (6%)

Incorrect
Correct answer
E

63%
Answered correctly

05 secs
Time Spent

2023
Version

Explanation

Noninsulin antidiabetic agents for type 2 diabetes mellitus		
Agent	**Mechanism of action**	**Adverse effects**
Insulin secretagogues • Sulfonylureas • Meglitinides	↑ Insulin secretion by inhibiting β-cell K_{ATP} channels	• Hypoglycemia • Weight gain
	Stimulate AMPK & inhibit mitochondrial	

https://t.me/USMLEWorldStep1

Noninsulin antidiabetic agents for type 2 diabetes mellitus		
Agent	**Mechanism of action**	**Adverse effects**
Insulin secretagogues • Sulfonylureas • Meglitinides	↑ Insulin secretion by inhibiting β-cell K_{ATP} channels	• Hypoglycemia • Weight gain
Biguanides • Metformin	Stimulate AMPK & inhibit mitochondrial gluconeogenesis, ↓ hepatic glucose production & ↑ peripheral glucose uptake	• Diarrhea • Lactic acidosis
Thiazolidinediones • Pioglitazone	Activate transcription regulator PPAR-γ, ↓ insulin resistance	• Fluid retention/heart failure • Weight gain
GLP-1 agonists • Exenatide • Liraglutide	↑ Glucose-dependent insulin secretion, ↓ glucagon secretion, delayed gastric emptying	• Pancreatitis • Weight loss
DPP4 inhibitors • Sitagliptin • Saxagliptin	↑ Endogenous GLP-1 & GIP levels	• Nasopharyngitis
SGLT-2 inhibitors • Canagliflozin • Dapagliflozin	↑ Renal glucose excretion	• Urinary tract infections • Hypotension

AMPK = AMP-activated protein kinase; **DPP4** = dipeptidyl peptidase-4; **GIP** = gastric inhibitory polypeptide; **GLP-1** = glucagon-like peptide-1; **K_{ATP}** = ATP-sensitive potassium; **PPAR-γ** = peroxisome proliferator–activated receptor γ; **SGLT-2** = sodium-glucose cotransporter-2.

Sodium-glucose cotransporter-2 (SGLT2) is a high-capacity transport protein that reabsorbs 90% of filtered

https://t.me/USMLEWorldStep1

Sodium-glucose cotransporter-2 (SGLT2) is a high-capacity transport protein that reabsorbs 90% of filtered glucose in the proximal tubule. **SGLT2 inhibitors** (eg, canagliflozin, dapagliflozin) are oral antidiabetic agents that decrease renal reabsorption of glucose and sodium, leading to urinary glucose loss and decreased blood glucose levels. The decreased reabsorption of sodium and glucose also induces **osmotic diuresis** and natriuresis, leading to a decrease in blood pressure and a lower rate of hospitalization for heart failure.

However, the glycosuria induced by SGLT2 inhibitors creates a more favorable environment for pathogenic bacteria and fungi in the genitourinary tract and perineum. This leads to an increased risk for **urinary tract infections** (eg, pyelonephritis), **genital mycotic infections** (eg, vaginitis), and **necrotizing fasciitis** of the perineum (ie, Fournier gangrene). Other adverse effects include hypovolemia, which can lead to orthostatic hypotension and acute kidney injury.

(Choice A) Glucagon-like peptide-1 agonists (eg, exenatide, dulaglutide) lower blood glucose levels by increasing glucose-dependent insulin secretion and suppressing glucagon secretion. Adverse effects include delayed gastric emptying and a possible increased risk for pancreatitis.

(Choice B) Thiazolidinediones (eg, pioglitazone) increase the reabsorption of sodium in the renal collecting tubule; this can lead to significant fluid retention, particularly in patients with heart failure. In contrast, SGLT2 inhibitors reduce fluid retention.

(Choices C and F) Exogenous insulin and sulfonylureas (eg, glimepiride), which stimulate endogenous insulin secretion, can cause hypoglycemia and weight gain. SGLT2 inhibitors carry a low risk for hypoglycemia because the glucose-lowering effect is proportionate to the filtered glucose load. In addition, renal glucose wasting typically induces mild weight loss.

(Choice D) Metformin inhibits hepatic gluconeogenesis, leading to the accumulation of lactate. Patients with decreased lactate clearance (eg, renal or hepatic dysfunction, congestive heart failure) can have excessive accumulation of lactate, leading to lactic acidosis.

Educational objective:
Sodium-glucose cotransporter-2 inhibitors (eg, canagliflozin, dapagliflozin) decrease renal reabsorption of glucose, leading to urinary glucose loss and decreased blood glucose levels. However, the resultant glycosuria can lead to

https://t.me/USMLEWorldStep1

levels. The decreased reabsorption of sodium and glucose also induces **osmotic diuresis** and natriuresis, leading to a decrease in blood pressure and a lower rate of hospitalization for heart failure.

However, the glycosuria induced by SGLT2 inhibitors creates a more favorable environment for pathogenic bacteria and fungi in the genitourinary tract and perineum. This leads to an increased risk for **urinary tract infections** (eg, pyelonephritis), **genital mycotic infections** (eg, vaginitis), and **necrotizing fasciitis** of the perineum (ie, Fournier gangrene). Other adverse effects include hypovolemia, which can lead to orthostatic hypotension and acute kidney injury.

(Choice A) Glucagon-like peptide-1 agonists (eg, exenatide, dulaglutide) lower blood glucose levels by increasing glucose-dependent insulin secretion and suppressing glucagon secretion. Adverse effects include delayed gastric emptying and a possible increased risk for pancreatitis.

(Choice B) Thiazolidinediones (eg, pioglitazone) increase the reabsorption of sodium in the renal collecting tubule; this can lead to significant fluid retention, particularly in patients with heart failure. In contrast, SGLT2 inhibitors reduce fluid retention.

(Choices C and F) Exogenous insulin and sulfonylureas (eg, glimepiride), which stimulate endogenous insulin secretion, can cause hypoglycemia and weight gain. SGLT2 inhibitors carry a low risk for hypoglycemia because the glucose-lowering effect is proportionate to the filtered glucose load. In addition, renal glucose wasting typically induces mild weight loss.

(Choice D) Metformin inhibits hepatic gluconeogenesis, leading to the accumulation of lactate. Patients with decreased lactate clearance (eg, renal or hepatic dysfunction, congestive heart failure) can have excessive accumulation of lactate, leading to lactic acidosis.

Educational objective:
Sodium-glucose cotransporter-2 inhibitors (eg, canagliflozin, dapagliflozin) decrease renal reabsorption of glucose, leading to urinary glucose loss and decreased blood glucose levels. However, the resultant glycosuria can lead to genitourinary tract infections and genital mycotic infections.

Pharmacology	Endocrine, Diabetes & Metabolism	Antidiabetic drugs
Subject	System	Topic

https://t.me/USMLEWorldStep1

SGLT-2 inhibitors • •		• Urinary tract infections

AM
1 =
SG

Sodiu
glucos
decrea
levels.
to a de

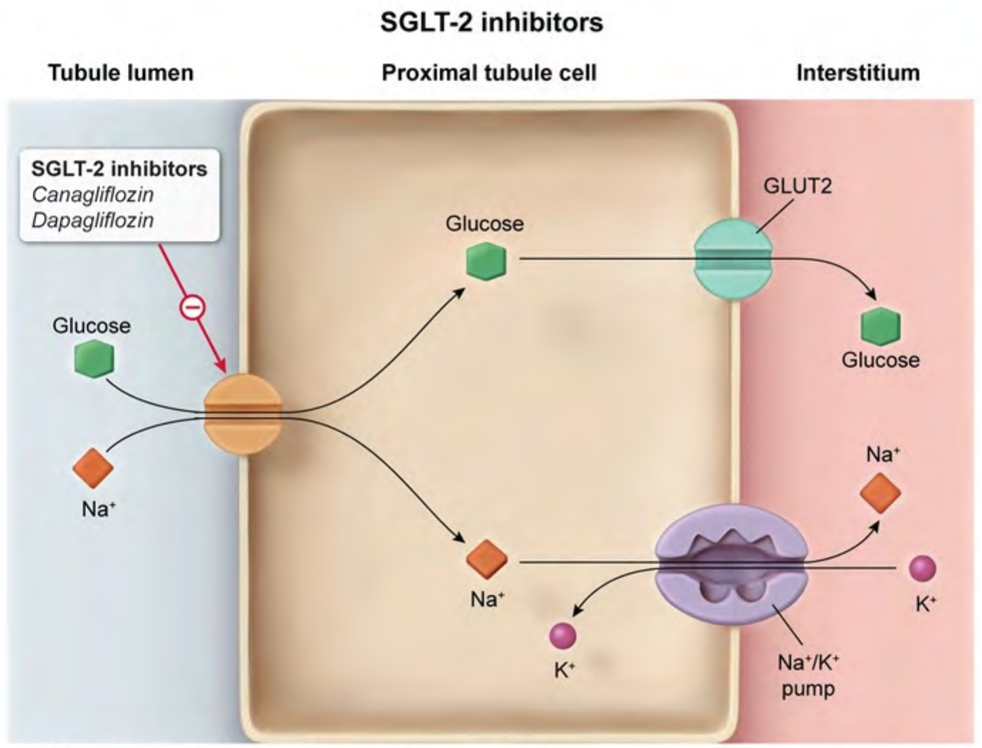
Howev
bacter
infecti
perine
hypote

(Choi
glucos
empty

(Choi
this ca
reduce

(Choi
secret
the glucose-lowering effect is proportionate to the filtered glucose load. In addition, renal glucose wasting typically induces mild weight loss.

Exhibit Display



GLUT2 = glucose transporter 2; **SGLT-2** = sodium-glucose cotransporter 2.

©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

A 34-year-old man comes to the clinic due to headaches and mild confusion over the past week. The patient has a seizure disorder and recently began taking carbamazepine. Vital signs are within normal limits. Physical examination shows no abnormalities. Laboratory studies reveal decreased serum sodium concentration. The patient is diagnosed with a condition caused by increased release of a hormone that is co-secreted with neurophysins. This hormone is most likely secreted into the systemic circulation at which of the following sites?

- A. Anterior lobe of pituitary gland
- B. Intermediate lobe of pituitary gland
- C. Median eminence of hypothalamus
- D. Paraventricular nucleus of hypothalamus
- E. Posterior lobe of pituitary gland
- F. Supraoptic nucleus of hypothalamus

Submit

https://t.me/USMLEWorldStep1

A 34-year-old man comes to the clinic due to headaches and mild confusion over the past week. The patient has a seizure disorder and recently began taking carbamazepine. Vital signs are within normal limits. Physical examination shows no abnormalities. Laboratory studies reveal decreased serum sodium concentration. The patient is diagnosed with a condition caused by increased release of a hormone that is co-secreted with neurophysins. This hormone is most likely secreted into the systemic circulation at which of the following sites?

- A. Anterior lobe of pituitary gland (6%)
- ✕ B. Intermediate lobe of pituitary gland (0%)
- C. Median eminence of hypothalamus (2%)
- D. Paraventricular nucleus of hypothalamus (7%)
- ✓ E. Posterior lobe of pituitary gland (67%)
- F. Supraoptic nucleus of hypothalamus (15%)

Incorrect
Correct answer
E

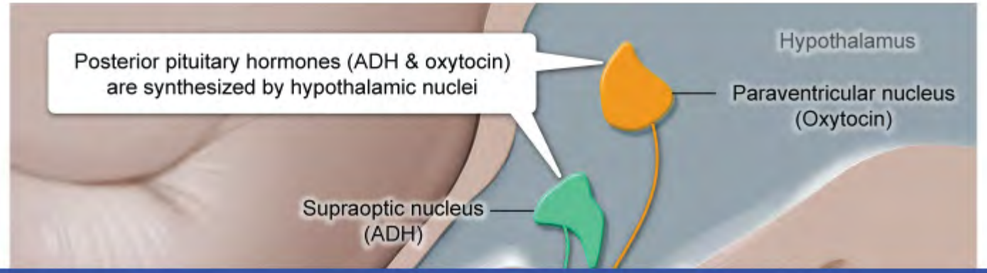
67%
Answered correctly

04 secs
Time Spent

2023
Version

Explanation

Posterior pituitary (neurohypophysis)

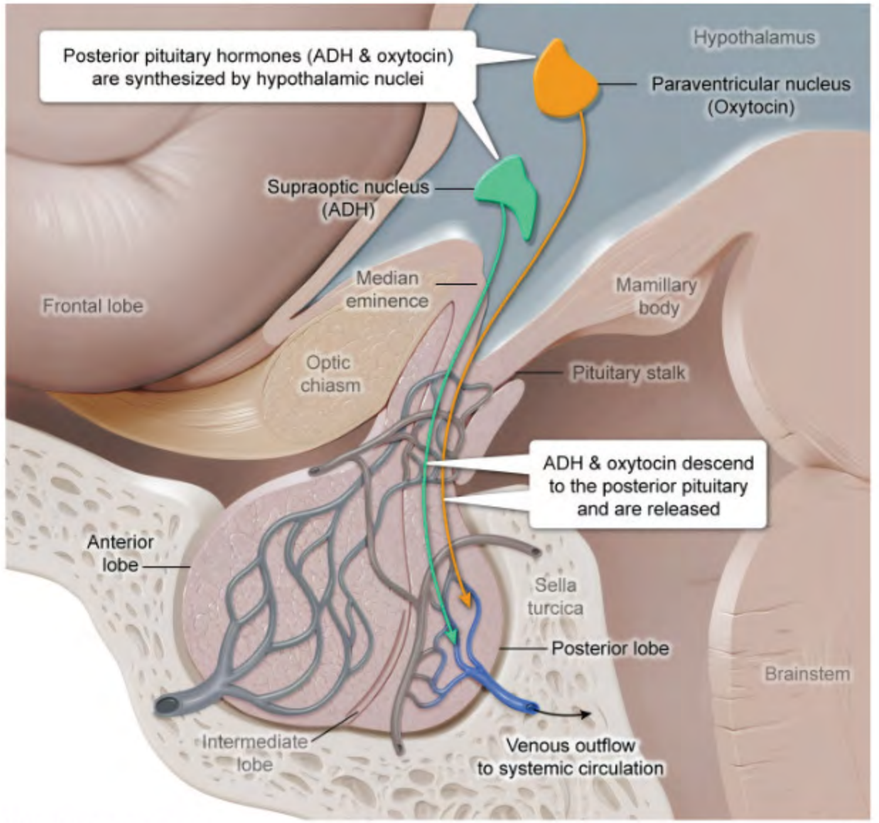


https://t.me/USMLEWorldStep1

A 34-year-old man comes to the clinic due to headaches and mild confusion over the past week. The patient has a seizur
exami
patien
neurop

Exhibit Display

Posterior pituitary (neurohypophysis)



ADH = Antidiuretic hormone (ie, vasopressin).

©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

ADH = Antidiuretic hormone (ie, vasopressin). ©UWorld

This patient with new-onset hyponatremia after drug exposure most likely has the syndrome of inappropriate antidiuretic hormone secretion (**SIADH**). This condition can be caused by a multitude of drugs, including **carbamazepine**, cyclophosphamide, and selective serotonin reuptake inhibitors.

Posterior pituitary hormones (eg, **ADH**, oxytocin) are **synthesized** within magnocellular neurons found in the supraoptic and paraventricular nuclei of the **hypothalamus**, with the former primarily producing ADH and the latter oxytocin **(Choices D and F)**. Once translated, these hormones are attached to carrier proteins known as neurophysins. The complexes are packaged into vesicles and travel down axon projections via anterograde transport into the posterior pituitary (neurohypophysis).

At their terminal endings, the axons become neurosecretory terminals known as Herring bodies, temporarily storing secretory vesicles. Pituicytes (glial cells) regulate the permeability of the hypophysial capillaries, facilitating **secretion** of ADH and oxytocin from the **posterior pituitary** into the hypophysial vein.

(Choice A) The anterior pituitary (adenohypophysis) is the glandular portion of the pituitary that lies closest to the optic chiasm. It is composed of various hormone-secreting cells, including lactotrophs (prolactin), corticotrophs (ACTH), somatotrophs (growth hormone), thyrotrophs (TSH), and gonadotrophs (FSH, LH).

(Choice B) The intermediate lobe of the pituitary gland is a vestigial region derived from the posterior wall of the Rathke pouch during embryonic development. Although predominantly nonfunctioning, the remainder produces melanocyte-stimulating hormone and endorphins.

(Choice C) The median eminence is a small ridge of hypothalamic tissue that secretes regulatory hormones (both releasing and inhibitory) that modulate the anterior pituitary. These include corticotropin-releasing hormone, gonadotropin releasing hormone, thyrotropin-releasing hormone, and growth hormone–releasing hormone.

Educational objective:
Vasopressin and oxytocin are synthesized and packaged with carrier proteins (neurophysins) within neurons found in the hypothalamus. The hormones are then transported down axonal projections to the posterior pituitary (neurohypophysis), where they are secreted into circulation.

https://t.me/USMLEWorldStep1

A 36-year-old man comes to the office due to skin lesions on his palms. The patient has yellowish skin nodules over the palmar creases that have been increasing in size and number over the past several years. He also has small clusters of yellow papules on his elbows, knees, and buttocks. His father died of a myocardial infarction at age 56. Biopsy of his lesions shows accumulation of lipid-laden macrophages. Immunoblot analysis suggests a lack of ApoE3 and ApoE4 in his circulating lipoproteins. Which of the following is most likely impaired in this patient?

- A. ApoC-2 production
- B. Cholesterol esterification in the blood
- C. Chylomicron remnant uptake by liver cells
- D. LDL particle uptake by hepatocytes
- E. Lipoprotein lipase activity

Submit

https://t.me/USMLEWorldStep1

A 36-year-old man comes to the office due to skin lesions on his palms. The patient has yellowish skin nodules over the palmar creases that have been increasing in size and number over the past several years. He also has small clusters of yellow papules on his elbows, knees, and buttocks. His father died of a myocardial infarction at age 56. Biopsy of his lesions shows accumulation of lipid-laden macrophages. Immunoblot analysis suggests a lack of ApoE3 and ApoE4 in his circulating lipoproteins. Which of the following is most likely impaired in this patient?

- ✗ A. ApoC-2 production (1%)
- B. Cholesterol esterification in the blood (7%)
- ✓ C. Chylomicron remnant uptake by liver cells (41%)
- D. LDL particle uptake by hepatocytes (35%)
- E. Lipoprotein lipase activity (13%)

Incorrect
Correct answer
C

41%
Answered correctly

05 secs
Time Spent

2023
Version

Explanation

Important inherited hyperlipoproteinemias			
Dyslipidemia	**Protein defect**	**Elevated lipoproteins**	**Major manifestations**
Familial chylomicronemia syndrome (type I)	• Lipoprotein lipase • ApoC-2	• Chylomicrons	• Acute pancreatitis • Lipemia retinalis • Eruptive xanthomas
Familial			• Premature atherosclerosis

https://t.me/USMLEWorldStep1

Important inherited hyperlipoproteinemias			
Dyslipidemia	**Protein defect**	**Elevated lipoproteins**	**Major manifestations**
Familial chylomicronemia syndrome (type I)	• Lipoprotein lipase • ApoC-2	• Chylomicrons	• Acute pancreatitis • Lipemia retinalis • Eruptive xanthomas
Familial hypercholesterolemia (type II A)	• LDL receptor • ApoB-100	• LDL	• Premature atherosclerosis • Tendon xanthomas • Xanthelasmas
Familial dysbetalipoproteinemia (type III)	• ApoE	• Chylomicron & VLDL remnants	• Premature atherosclerosis • Tuboeruptive & palmar xanthomas
Familial hypertriglyceridemia (type IV)	• Polygenic	• VLDL	• Associated with coronary disease, pancreatitis & diabetes

Familial dysbetalipoproteinemia (type III hyperlipoproteinemia) is characterized by xanthomas and premature coronary and peripheral vascular disease. It is an autosomal recessive disorder that is clinically more severe in patients with other conditions affecting lipoprotein metabolism (eg, diabetes, hypothyroidism).

The primary defects in familial dysbetalipoproteinemia are in **ApoE3 and ApoE4**, apolipoproteins found on the triglyceride-rich lipoproteins (**chylomicrons and VLDLs**) that are responsible for binding hepatic apolipoprotein receptors. Without ApoE3 and ApoE4, the liver cannot efficiently remove chylomicrons and VLDL remnants from the circulation, causing their accumulation in the blood and resultant elevations in **cholesterol and triglyceride** levels.

https://t.me/USMLEWorldStep1

			diabetes

Familial dysbetalipoproteinemia (type III hyperlipoproteinemia) is characterized by xanthomas and premature coronary and peripheral vascular disease. It is an autosomal recessive disorder that is clinically more severe in patients with other conditions affecting lipoprotein metabolism (eg, diabetes, hypothyroidism).

The primary defects in familial dysbetalipoproteinemia are in **ApoE3 and ApoE4**, apolipoproteins found on the triglyceride-rich lipoproteins (**chylomicrons and VLDLs**) that are responsible for binding hepatic apolipoprotein receptors. Without ApoE3 and ApoE4, the liver cannot efficiently remove chylomicrons and VLDL remnants from the circulation, causing their accumulation in the blood and resultant elevations in **cholesterol and triglyceride** levels.

(Choices A and E) Familial chylomicronemia syndrome is an autosomal recessive disorder characterized by defective lipoprotein lipase activity with increased synthesis and decreased clearance of chylomicron particles (and VLDL to a lesser extent). It can also be due to ApoC2 deficiency because lipoprotein lipase is activated by ApoC2 on chylomicrons and VLDL.

(Choice B) ApoA1 is required for esterification of free cholesterol in HDL particles by lecithin-cholesterol acyltransferase (LCAT). ApoA1 and LCAT deficiencies result in low HDL levels and increased circulating free cholesterol levels.

(Choice D) Familial hypercholesterolemia is associated with increased levels of LDL cholesterol. It is caused by defects in the ApoB/E LDL receptor or ApoB-100 ligand, leading to decreased hepatic clearance of LDL.

Educational objective:
Familial dysbetalipoproteinemia (type III hyperlipoproteinemia) is an autosomal recessive disorder characterized by elevated cholesterol and triglyceride levels. It is caused by defects in ApoE3 and ApoE4, leading to decreased clearance of chylomicrons and VLDL remnants. Patients can develop eruptive and palmar xanthomas and premature atherosclerosis.

Biochemistry Endocrine, Diabetes & Metabolism Dyslipidemia

https://t.me/USMLEWorldStep1

A 35-year-old man comes to the office for evaluation of an enlarged left testis. He also reports decreased libido and erectile potency for the last 2 months. The patient has no chronic medical conditions and takes no medications. Physical examination is notable for significant enlargement of the left testis and bilateral gynecomastia. His other secondary sexual characteristics are normal. Serum β-hCG is markedly elevated and serum TSH is normal. Scrotal ultrasound reveals a 3.1-cm, irregular testicular mass with cystic areas. Which of the following is the most likely cause of this patient's gynecomastia?

- A. Decreased adrenal androgen production
- B. Decreased hypothalamic secretion of GnRH
- C. Displacement of androgens from breast androgen receptors
- D. Increased Leydig cell aromatase activity

Submit

https://t.me/USMLEWorldStep1

A 35-year-old man comes to the office for evaluation of an enlarged left testis. He also reports decreased libido and erectile potency for the last 2 months. The patient has no chronic medical conditions and takes no medications. Physical examination is notable for significant enlargement of the left testis and bilateral gynecomastia. His other secondary sexual characteristics are normal. Serum β-hCG is markedly elevated and serum TSH is normal. Scrotal ultrasound reveals a 3.1-cm, irregular testicular mass with cystic areas. Which of the following is the most likely cause of this patient's gynecomastia?

- A. Decreased adrenal androgen production (5%)
- ✗ B. Decreased hypothalamic secretion of GnRH (21%)
- C. Displacement of androgens from breast androgen receptors (5%)
- ✓ D. Increased Leydig cell aromatase activity (67%)

Incorrect
Correct answer
D

67%
Answered correctly

04 secs
Time Spent

2023
Version

Explanation

Causes of gynecomastia in adults	
Physiologic gynecomastia	• Decreased T synthesis with aging • Increased aromatization of androgens in adipose tissue
Hypogonadism	• Low-circulating T levels • Uninterrupted adrenal production of E precursors (high E/T ratio)
Cirrhosis	• Decreased hepatic clearance of Es
	• Spironolactone, antiandrogens (eg, flutamide) & cimetidine: androgen receptor antagonism

https://t.me/USMLEWorldStep1

Explanation

Causes of gynecomastia in adults	
Physiologic gynecomastia	• Decreased T synthesis with aging • Increased aromatization of androgens in adipose tissue
Hypogonadism	• Low-circulating T levels • Uninterrupted adrenal production of E precursors (high E/T ratio)
Cirrhosis	• Decreased hepatic clearance of Es
Medications	• Spironolactone, antiandrogens (eg, flutamide) & cimetidine: androgen receptor antagonism • 5AR inhibitors (eg, finasteride): decreased conversion of T to DHT • Ketoconazole: decreased T synthesis • GnRH agonists: suppression of pituitary-gonadal axis • Androgenic steroids: increased aromatization to Es
Testicular tumors	• hCG secretion by germ cell tumor • Impaired T production and increased aromatization in Leydig cells
Hyperthyroidism	• Increased LH secretion • Increased aromatization of androgens
5AR = 5-alpha reductase; **DHT** = dihydrotestosterone; **E** = estrogen; **T** = testosterone.	

Gynecomastia is abnormal growth of breast tissue in males. It is generally due to an **increased ratio of estrogens** (which cause hyperplasia of breast ductal epithelium and increased fibrosis of stromal tissues) to androgens (which have an inhibitory effect on breast development).

In addition to gynecomastia, this patient has hypogonadal symptoms (eg, decreased libido, erectile dysfunction) that suggest decreased testicular androgen production. In light of the large testicular mass and elevated β-hCG level, this likely represents an **hCG-secreting germ cell tumor** of the testis. Excessive secretion of hCG by

https://t.me/USMLEWorldStep1

	• Increased aromatization of androgens
5AR = 5-alpha reductase; **DHT** = dihydrotestosterone; **E** = estrogen; **T** = testosterone.	

Gynecomastia is abnormal growth of breast tissue in males. It is generally due to an **increased ratio of estrogens** (which cause hyperplasia of breast ductal epithelium and increased fibrosis of stromal tissues) to androgens (which have an inhibitory effect on breast development).

In addition to gynecomastia, this patient has hypogonadal symptoms (eg, decreased libido, erectile dysfunction) that suggest decreased testicular androgen production. In light of the large testicular mass and elevated β-hCG level, this likely represents an **hCG-secreting germ cell tumor** of the testis. Excessive secretion of hCG by testicular germ cell tumors **suppresses testosterone production** in Leydig cells while **increasing aromatase activity** and conversion of testosterone to estradiol; the resulting increase in the estrogen/androgen ratio can cause gynecomastia.

(Choice A) Inadequate production of adrenal androgens (eg, dehydroepiandrosterone [DHEA], DHEA-sulfate) is seen in patients with 17-alpha-hydroxylase deficiency. In males, this condition usually manifests in childhood with undervirilization and ambiguous (or female) external genitalia.

(Choice B) Decreased hypothalamic secretion of GnRH suppresses the entire GnRH-pituitary-gonadal axis, leading to decreased testosterone production. Concurrently, aromatization of weak adrenal androgens to estrogens maintains estrogen levels proportionally high, leading to gynecomastia. However, gynecomastia in patients with germ cell tumors is primarily due to Leydig cell aromatization of androgens.

(Choice C) A number of drugs (eg, spironolactone, flutamide, cimetidine) inhibit binding of testosterone and dihydrotestosterone to the androgen receptor, leading to gynecomastia. However, hCG does not affect androgen binding.

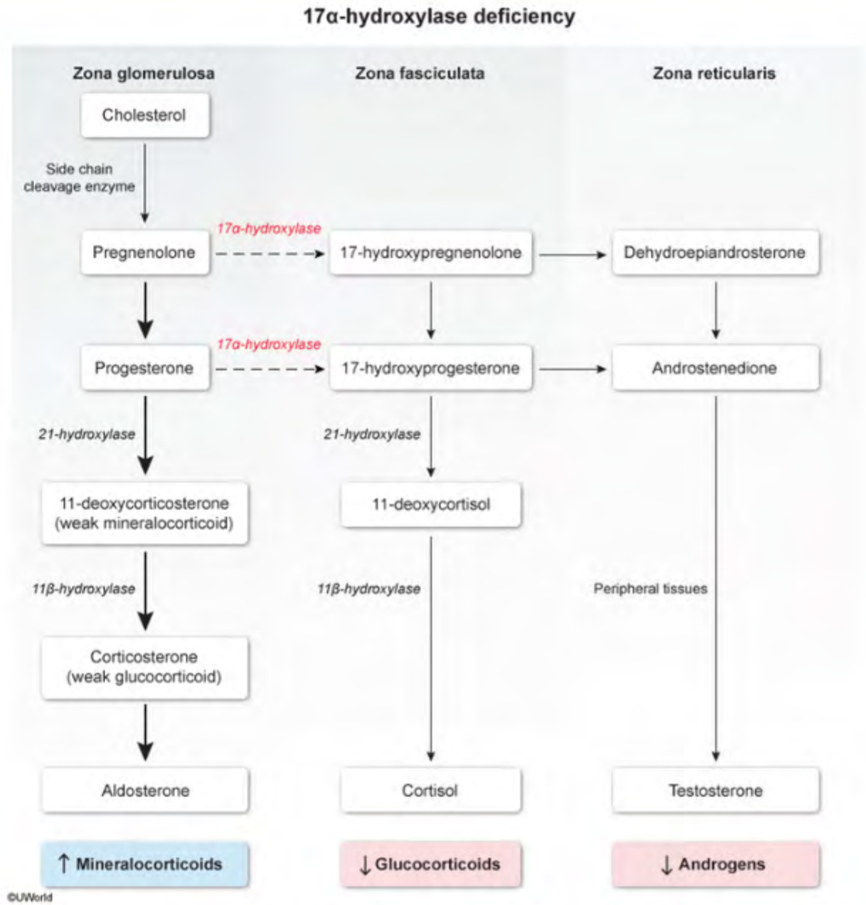
Educational objective:
Secretion of hCG by testicular germ cell tumors impairs testosterone production in Leydig cells while increasing aromatase activity and conversion of androgens to estrogens. The resulting increase in the estrogen/androgen ratio can cause gynecomastia.

Physiology Endocrine, Diabetes & Metabolism Testicular cancer

https://t.me/USMLEWorldStep1

	• Increased aromatization of androgens
5A	

Exhibit Display

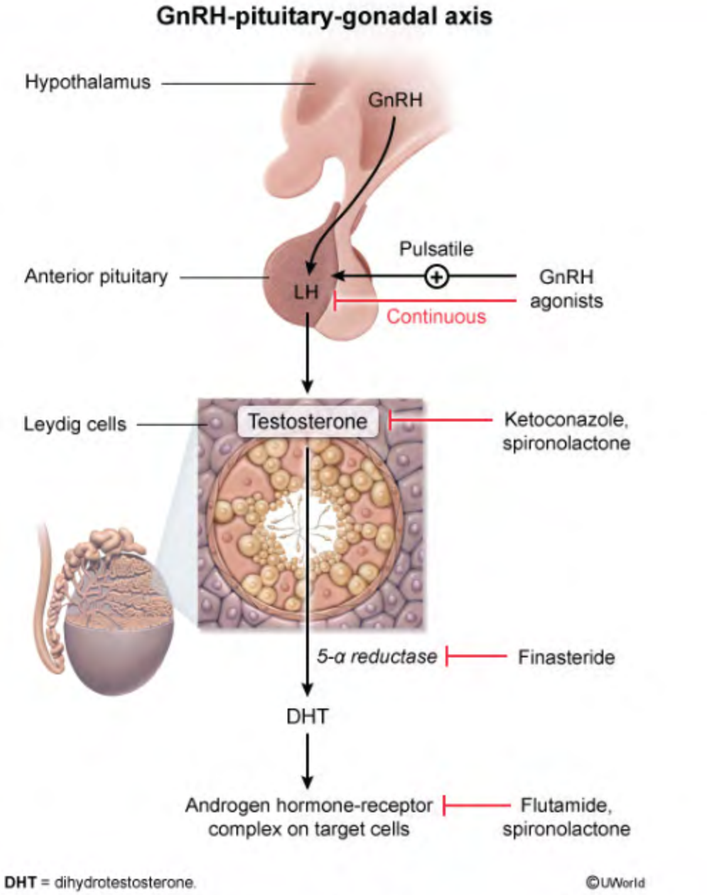


Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

	• Increased aromatization of androgens
5A	

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

A 26-year-old man comes to the emergency department due to a 10-hour history of progressively worsening right-sided scrotal pain. Clinical and radiological evaluations confirm testicular torsion with significant ischemic damage and the patient undergoes unilateral orchiectomy. Three months later, he comes to the office for follow-up. The patient is otherwise healthy and takes no medications but is worried about the risk of sexual dysfunction and infertility. Further evaluation is most likely to show which of the following sets of findings in this patient?

	Erectile function	Sperm count
A.	Decreased	Decreased
B.	Normal	Decreased
C.	Normal	Normal
D.	Decreased	Normal

Submit

https://t.me/USMLEWorldStep1

A 26-year-old man comes to the emergency department due to a 10-hour history of progressively worsening right-sided scrotal pain. Clinical and radiological evaluations confirm testicular torsion with significant ischemic damage and the patient undergoes unilateral orchiectomy. Three months later, he comes to the office for follow-up. The patient is otherwise healthy and takes no medications but is worried about the risk of sexual dysfunction and infertility. Further evaluation is most likely to show which of the following sets of findings in this patient?

	Erectile function	Sperm count	
✗ A.	Decreased	Decreased	(1%)
✓ B.	Normal	Decreased	(59%)
C.	Normal	Normal	(38%)
D.	Decreased	Normal	(1%)

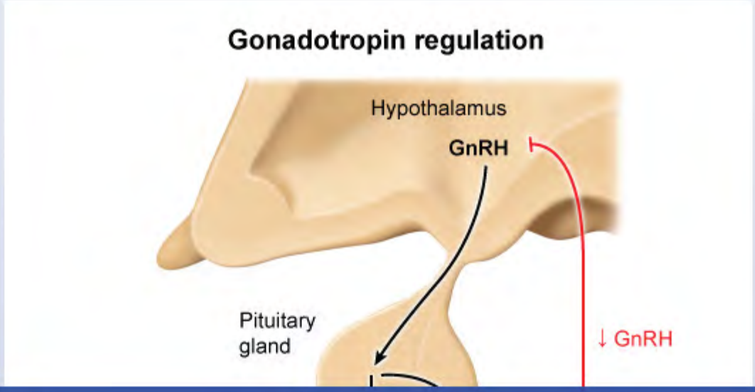
Incorrect
Correct answer
B

59%
Answered correctly

04 secs
Time Spent

2023
Version

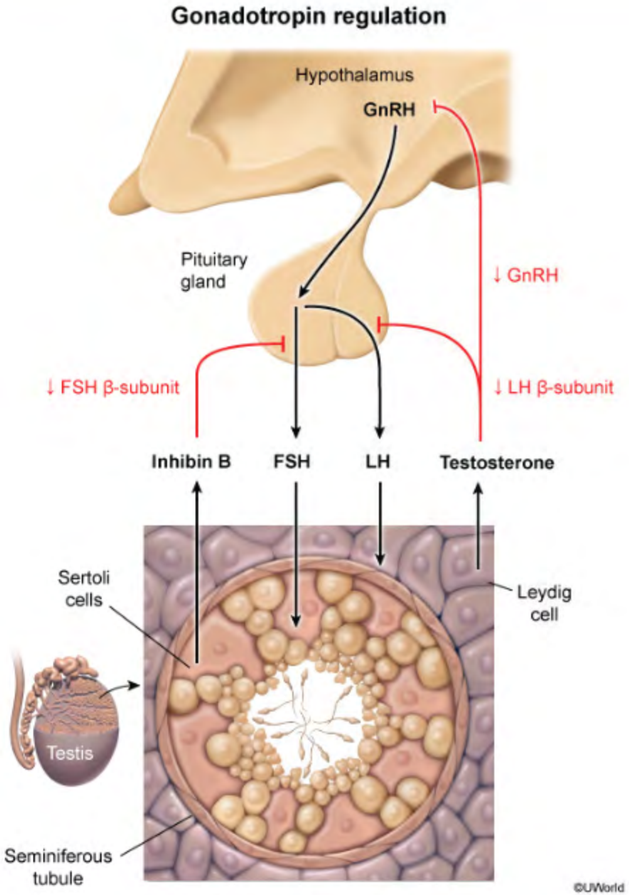
Explanation



https://t.me/USMLEWorldStep1

A 26-year-old man comes to the emergency department due to a 10-hour history of progressively worsening right-sided
damag
up. Th
and int

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

tubule



©UWorld

Spermatogenesis in the testis is dependent on 2 primary hormone systems. Testicular Leydig cells produce **testosterone** in response to LH from the pituitary; in turn, LH is regulated by feedback inhibition from testosterone. At the same time, FSH from the pituitary induces the Sertoli cells to produce androgen binding protein (ABP), which concentrates testosterone in the seminiferous tubules and facilitates spermatogenesis. The Sertoli cells also produce inhibin, which provides feedback regulation of FSH.

Following **unilateral orchiectomy**, the initial drop in circulating testosterone stimulates pituitary LH secretion, leading to **compensatory testosterone production** and Leydig cell hyperplasia in the remaining testis. Testosterone levels are quickly restored, maintaining normal libido, erectile function, and secondary sex characteristics.

Concurrently, the loss of inhibin following unilateral orchiectomy leads to increased pituitary FSH release, stimulating ABP production and facilitating spermatogenesis in the remaining testis. However, due to the **loss of seminiferous tubules** in the orchiectomized testis, most patients experience **decreased net spermatogenesis**, often with reduced fertility **(Choice C)**.

(Choice A) Bilateral testicular damage (eg, orchitis, bilateral orchiectomy) leads to azoospermia. In addition, nontesticular sources of testosterone (eg, adrenals) are often inadequate to maintain normal libido and erectile function.

(Choice D) Erectile dysfunction (ED) with normal sperm counts can be caused by a variety of disorders (eg, neurologic or vascular disorders, psychogenic ED), but most patients who have loss of testosterone production severe enough to cause ED will also have impaired spermatogenesis.

Educational objective:
Following unilateral orchiectomy, the drop in testosterone stimulates pituitary LH secretion, which stimulates increased testosterone production in the remaining testis and maintains libido, erectile function, and secondary sex characteristics. However, the loss of sperm-producing tissue usually causes a drop in sperm counts.

Physiology	Endocrine, Diabetes & Metabolism	Male sexual dysfunction
Subject	System	Topic

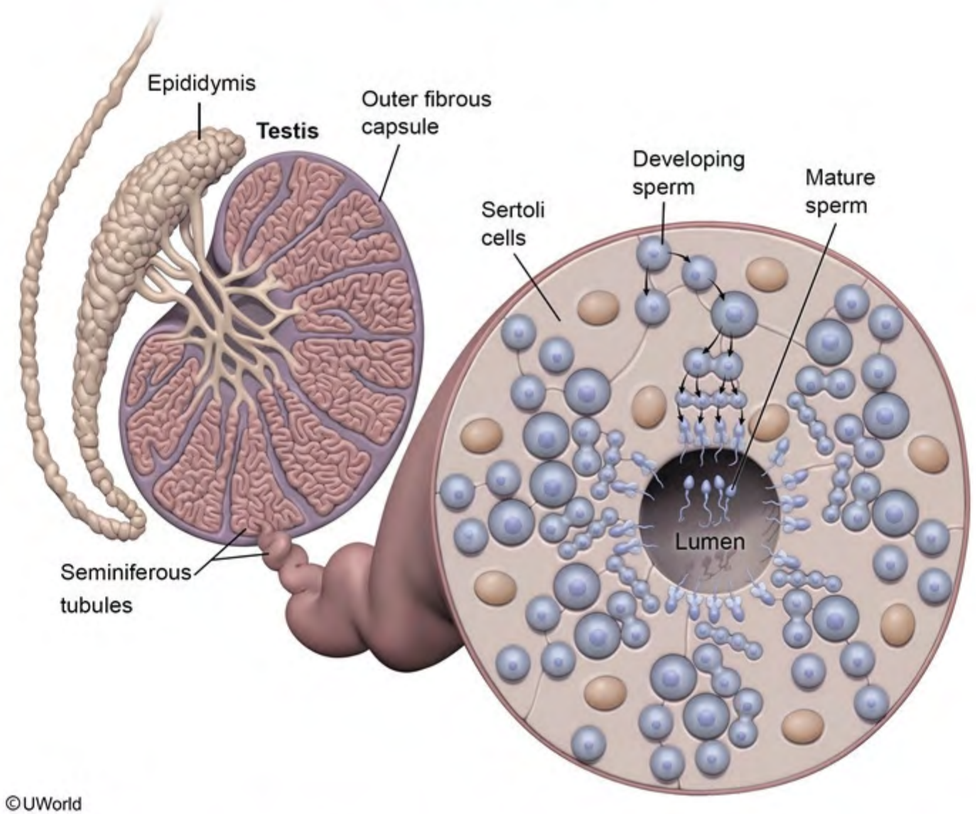
https://t.me/USMLEWorldStep1

tubule

©UWorld

Exhibit Display

Spermatogenesis



©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Physiology
Subject

Endocrine, Diabetes & Metabolism
System

Male sexual dysfunction
Topic

https://t.me/USMLEWorldStep1

A 32-year-old woman comes to the office due to a persistent sensation of warmth. For the last 6 months she has felt unusually warm compared to others in the room. The patient has no medical problems and takes no medications or supplements. She does not use tobacco, alcohol, or illicit drugs. Family history is significant for hypothyroidism in her mother. Temperature is 36.7 C (98 F), blood pressure is 130/60 mm Hg, and pulse is 104/min. BMI is 20 kg/m^2. On physical examination, the patient appears anxious and has a staring gaze. There is exophthalmos, lid lag, and a diffusely enlarged thyroid with an audible thyroid bruit. The patient has a fine tremor on outstretched arms, and the skin is warm and moist. Antibodies directed against which of the following are most likely to be found in this patient?

- A. Thyroglobulin
- B. Thyroid peroxidase
- C. Thyrotropin receptor
- D. Thyroxine
- E. Triiodothyronine

Submit

https://t.me/USMLEWorldStep1

A 32-year-old woman comes to the office due to a persistent sensation of warmth. For the last 6 months she has felt unusually warm compared to others in the room. The patient has no medical problems and takes no medications or supplements. She does not use tobacco, alcohol, or illicit drugs. Family history is significant for hypothyroidism in her mother. Temperature is 36.7 C (98 F), blood pressure is 130/60 mm Hg, and pulse is 104/min. BMI is 20 kg/m^2. On physical examination, the patient appears anxious and has a staring gaze. There is exophthalmos, lid lag, and a diffusely enlarged thyroid with an audible thyroid bruit. The patient has a fine tremor on outstretched arms, and the skin is warm and moist. Antibodies directed against which of the following are most likely to be found in this patient?

- ✗ A. Thyroglobulin (9%)
- B. Thyroid peroxidase (12%)
- ✓ C. Thyrotropin receptor (77%)
- D. Thyroxine (0%)
- E. Triiodothyronine (0%)

Incorrect
Correct answer
C

77%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

Thyroid autoantibodies	
Antibody	**Disease association**
Thyrotropin (TSH) receptor antibody	• Graves disease • Functional bioassay (thyroid-stimulating immunoglobulin) is also available
	• Chronic lymphocytic (Hashimoto) thyroiditis

https://t.me/USMLEWorldStep1

Explanation

Thyroid autoantibodies	
Antibody	**Disease association**
Thyrotropin (TSH) receptor antibody	• Graves disease • Functional bioassay (thyroid-stimulating immunoglobulin) is also available
Thyroid peroxidase antibody	• Chronic lymphocytic (Hashimoto) thyroiditis • Silent thyroiditis • Postpartum thyroiditis • Some patients with Graves disease
Thyroglobulin antibody	• Nonspecific, but more common in hypothyroidism than hyperthyroidism

This patient has signs of hyperthyroidism, including heat intolerance, tachycardia, and lid lag. In light of her diffuse goiter and exophthalmos this is very likely due to **Graves disease**. Graves disease is an autoimmune disorder triggered by **thyrotropin receptor antibodies** (TRAb), which bind and activate the TSH receptor. In addition to the thyroid, the TSH receptor antigen is present on other cell types, including fibroblasts and adipocytes. Graves ophthalmopathy is characterized by ocular irritation, impaired extraocular motion, and proptosis; it is caused by T-cell activation and stimulation of orbital fibroblasts by TRAb, leading to expansion of extraocular muscles and retro-orbital tissues.

TRAb binds to extracellular domains on the TSH receptor, a transmembrane G protein–coupled receptor. The G_s alpha subunit activates adenylate cyclase and subsequently the adenylate cyclase second messenger system. Serum TRAb immunoassays have a high sensitivity (97%) and specificity (99%) for Graves disease, although they detect both activating and blocking anti-TSH receptor antibodies. Activating antibodies can be confirmed with a functional bioassay (thyroid-stimulating immunoglobulin) that measures cyclic AMP production by a TSH-receptor–expressing cell line in response to patient serum.

(Choice A) Antibodies to thyroglobulin are thought to reflect disruption of thyroid follicles, which exposes

https://t.me/USMLEWorldStep1

This patient has signs of hyperthyroidism, including heat intolerance, tachycardia, and lid lag. In light of her diffuse goiter and exophthalmos this is very likely due to **Graves disease**. Graves disease is an autoimmune disorder triggered by **thyrotropin receptor antibodies** (TRAb), which bind and activate the TSH receptor. In addition to the thyroid, the TSH receptor antigen is present on other cell types, including fibroblasts and adipocytes. Graves ophthalmopathy is characterized by ocular irritation, impaired extraocular motion, and proptosis; it is caused by T-cell activation and stimulation of orbital fibroblasts by TRAb, leading to expansion of extraocular muscles and retro-orbital tissues.

TRAb binds to extracellular domains on the TSH receptor, a transmembrane G protein–coupled receptor. The G_s alpha subunit activates adenylate cyclase and subsequently the adenylate cyclase second messenger system. Serum TRAb immunoassays have a high sensitivity (97%) and specificity (99%) for Graves disease, although they detect both activating and blocking anti-TSH receptor antibodies. Activating antibodies can be confirmed with a functional bioassay (thyroid-stimulating immunoglobulin) that measures cyclic AMP production by a TSH-receptor–expressing cell line in response to patient serum.

(Choice A) Antibodies to thyroglobulin are thought to reflect disruption of thyroid follicles, which exposes thyroglobulin to the bloodstream. They are present in a number of autoimmune thyroid disorders but are most common in autoimmune hypothyroidism and are present in only a minority of patients with Graves disease.

(Choice B) Thyroid peroxidase antibodies are most closely associated with Hashimoto thyroiditis and related disorders (eg, silent thyroiditis, postpartum thyroiditis). Hyperthyroidism with exophthalmos is most consistent with Graves disease.

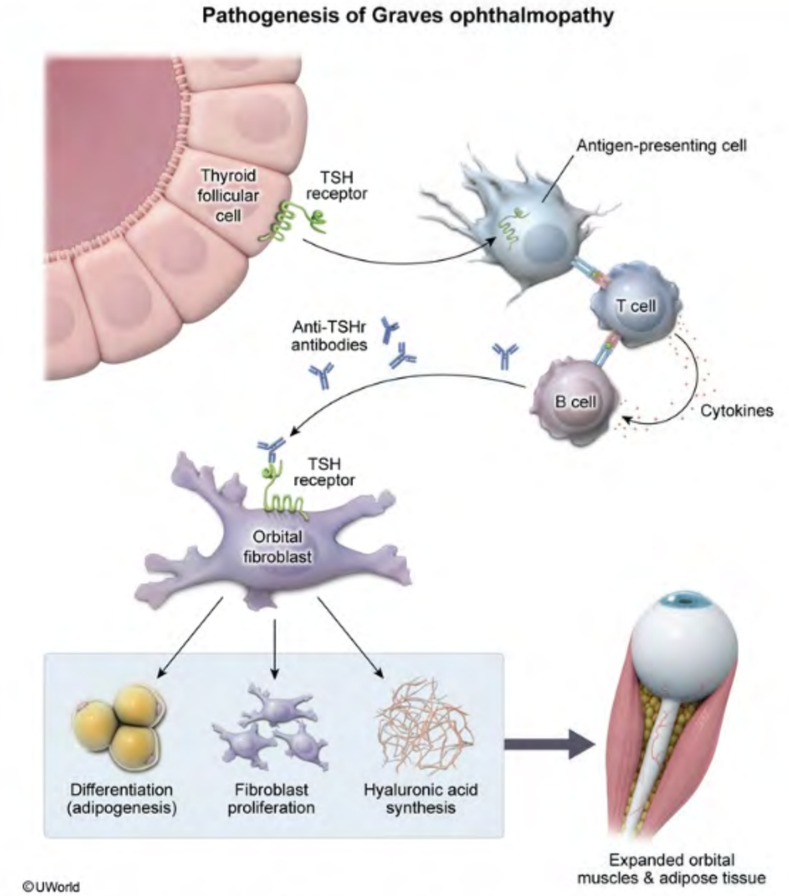
(Choices D and E) Antibodies to thyroxine and triiodothyronine (ie, anti-T4 and anti-T3 immunoglobulins, respectively) can be detected by adding radiolabeled thyroid hormone to the patient's serum followed by precipitation of the antigen-antibody complexes with polyethylene glycol. These antibodies can be seen in a variety of autoimmune thyroid disorders, but are rare.

Educational objective:
Graves disease is an autoimmune disorder triggered by thyrotropin receptor antibodies (TRAb) that bind and activate the TSH receptor. Serum TRAb immunoassays have a high sensitivity and specificity for Graves disease.

https://t.me/USMLEWorldStep1

antibody	• Postpartum thyroiditis • Some patients with Graves disease

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

This p
goiter
trigger
the thy
ophtha
cell ac
orbital

TRAb
alpha
Serum
detect
functio
expres

(Choi
thyrog
comm

(Choi
disord
Grave

(Choi
respec
precip
variety of autoimmune thyroid disorders, but are rare.

https://t.me/USMLEWorldStep1

antibody	• Postpartum thyroiditis • Some patients with Graves disease

Exhibit Display

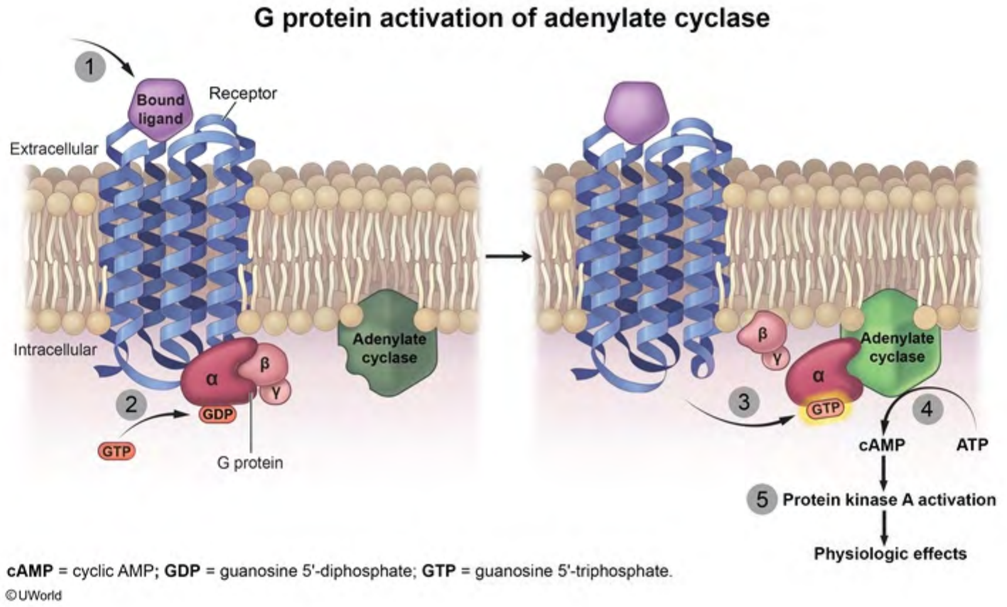
This p
goiter
trigger
the thy
ophtha
cell ac
orbital

TRAb
alpha
Serum
detect
functio
expres

(Choi
thyrog
comm

(Choi
disord
Grave

(Choi
respec
precip
variety of autoimmune thyroid disorders, but are rare.



Zoom In Zoom Out Reset New | Existing My Notebook

A 62-year-old woman is brought to the emergency department after a fall and is found to have a left femoral neck fracture. The patient is admitted to the hospital, and a hip arthroplasty is planned. Medical history is significant for long-standing type 2 diabetes mellitus, hypertension, hyperlipidemia, and migraines. While hospitalized, the patient receives a combination of long- and short-acting insulin for diabetes management. On the morning of surgery, fasting blood glucose level is 42 mg/dL. The patient is awake and alert and says she feels hungry but has no other symptoms of hypoglycemia. Concurrent use of which of the following medications best explains this finding?

- A. Atorvastatin
- B. Doxazosin
- C. Hydrochlorothiazide
- D. Losartan
- E. Propranolol
- F. Verapamil

Submit

https://t.me/USMLEWorldStep1

A 62-year-old woman is brought to the emergency department after a fall and is found to have a left femoral neck fracture. The patient is admitted to the hospital, and a hip arthroplasty is planned. Medical history is significant for long-standing type 2 diabetes mellitus, hypertension, hyperlipidemia, and migraines. While hospitalized, the patient receives a combination of long- and short-acting insulin for diabetes management. On the morning of surgery, fasting blood glucose level is 42 mg/dL. The patient is awake and alert and says she feels hungry but has no other symptoms of hypoglycemia. Concurrent use of which of the following medications best explains this finding?

- ✗ A. Atorvastatin (6%)
- B. Doxazosin (6%)
- C. Hydrochlorothiazide (16%)
- D. Losartan (4%)
- ✓ E. Propranolol (63%)
- F. Verapamil (2%)

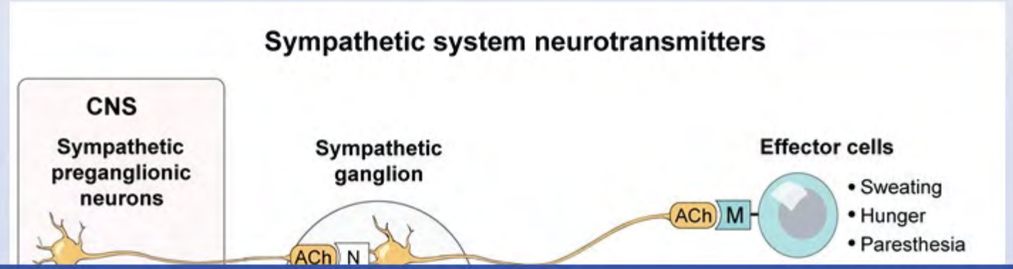
Incorrect
Correct answer
E

63%
Answered correctly

31 secs
Time Spent

2023
Version

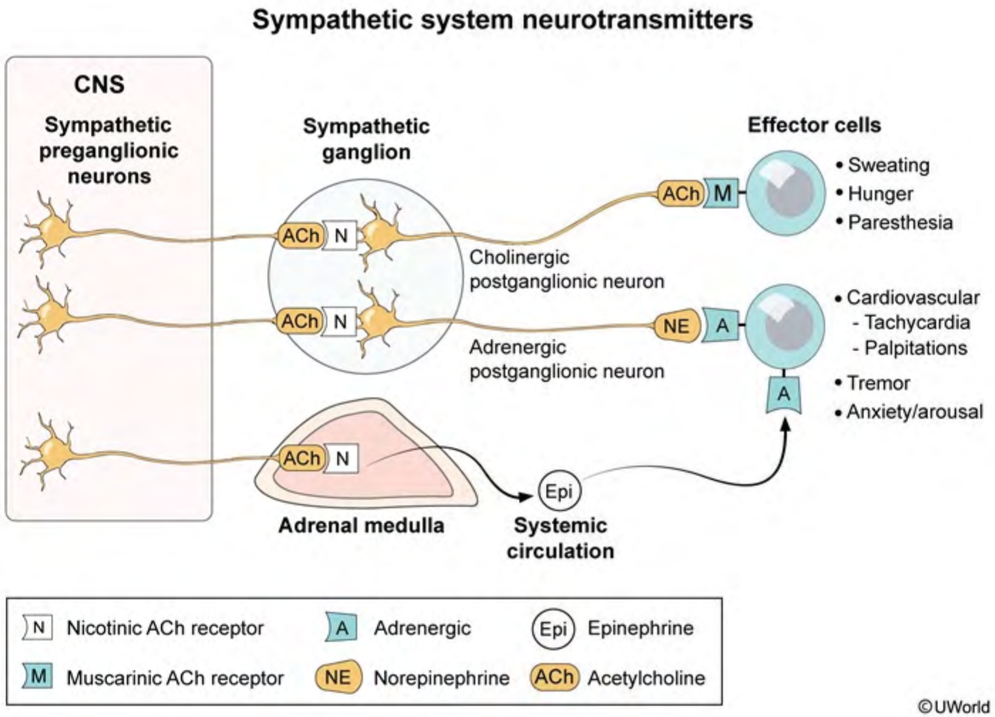
Explanation



https://t.me/USMLEWorldStep1

A 62-year-old woman is brought to the emergency department after a fall and is found to have a left femoral neck
fractur
long-s
patien
surger
no oth
finding

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Prolonged hypoglycemia can lead to irreversible neurologic deficits and death. To prevent injury, counterregulatory systems raise blood glucose in response to hypoglycemia via sympathetic nervous system activation (ie, norepinephrine/**epinephrine** release) and increase secretion of **glucagon**, cortisol, and growth hormone.

Symptoms of hypoglycemia fall into 2 general categories: neurogenic (autonomic) and neuroglycopenic.

- **Neurogenic symptoms** are mediated via norepinephrine/epinephrine and acetylcholine release during sympathetic stimulation. Symptoms due to **norepinephrine/epinephrine** include tremulousness, tachycardia, and anxiety/arousal, whereas **acetylcholine** causes sweating, hunger, and paresthesias.
- **Neuroglycopenic symptoms** are due to inadequate availability of glucose in the CNS and include behavioral changes, confusion, visual disturbances, stupor, and seizures.

This patient has **reduced awareness** of hypoglycemia, likely due to the use of a **nonselective beta blocker** (eg, propranolol) for chronic treatment of migraines and/or hypertension. Nonselective beta blockers attenuate the norepinephrine/epinephrine-mediated symptoms of hypoglycemia, but cholinergic symptoms (eg, hunger) are unaffected. In addition, nonselective beta blockers can contribute to the severity of hypoglycemia; epinephrine stimulates hepatic gluconeogenesis and peripheral glycogenolysis, but this effect is diminished by nonselective beta blockers.

(Choices A and C) Statins (eg, atorvastatin) and hydrochlorothiazide can increase blood glucose levels but would not mask symptoms of hypoglycemia.

(Choice B) Insulin-secreting pancreatic beta cells have alpha-2 and beta-2 receptors; stimulation of alpha-2 receptors inhibits insulin secretion, whereas stimulation of beta-2 receptors increases insulin secretion. Doxazosin is a selective alpha-1 blocker and has no effect on glucose levels.

(Choices D and F) Angiotensin II receptor blockers (eg, losartan) and nondihydropyridine calcium channel blockers (eg, verapamil) do not mask the symptoms of hypoglycemia and have virtually no effect on glucose levels.

Educational objective:
Nonselective beta blockers exacerbate hypoglycemia and mask hypoglycemic symptoms mediated by norepinephrine/epinephrine.

References

https://t.me/USMLEWorldStep1

A 23-year-old man is brought to the emergency department by paramedics following a motor vehicle accident. He was an unrestrained passenger in the front seat. Several days after hospitalization, his fluid volume and plasma osmolarity are measured and illustrated in the image below (solid line, normal; dotted line, patient).

Which of the following conditions is most likely to cause the findings shown in the image?

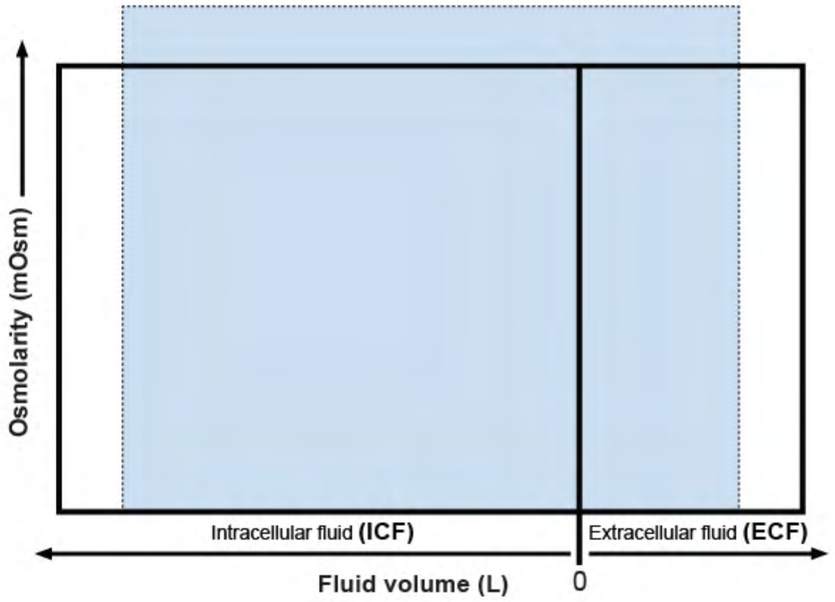
- A. Acute gastrointestinal hemorrhage
- B. Adrenal insufficiency
- C. Diabetes insipidus
- D. Hypertonic saline infusion
- E. Primary polydipsia

Submit

https://t.me/USMLEWorldStep1

A 23-year-old man is brought to the emergency department by paramedics following a motor vehicle accident. He was ar
osmol

Exhibit Display



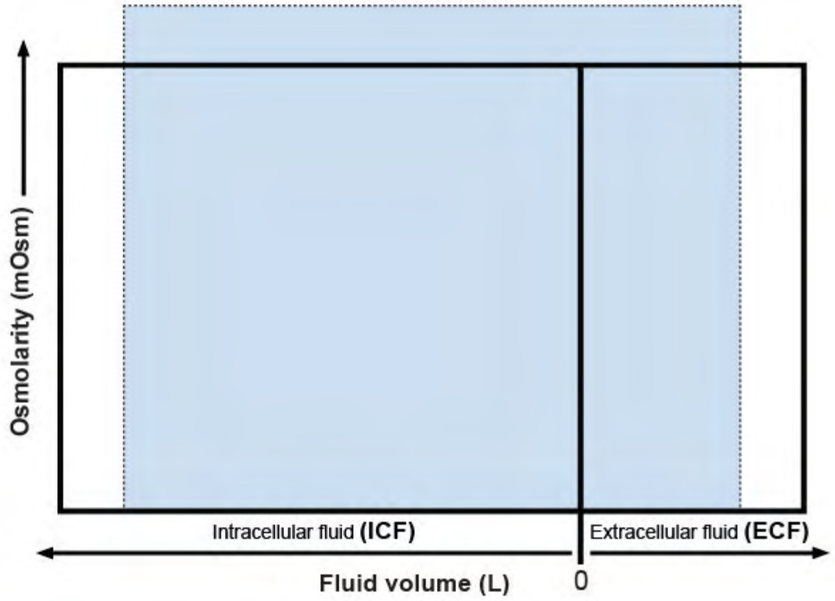
©UWorld

Zoom In Zoom Out Reset New | Existing My Notebook

Which

C. Diabetes insipidus

https://t.me/USMLEWorldStep1



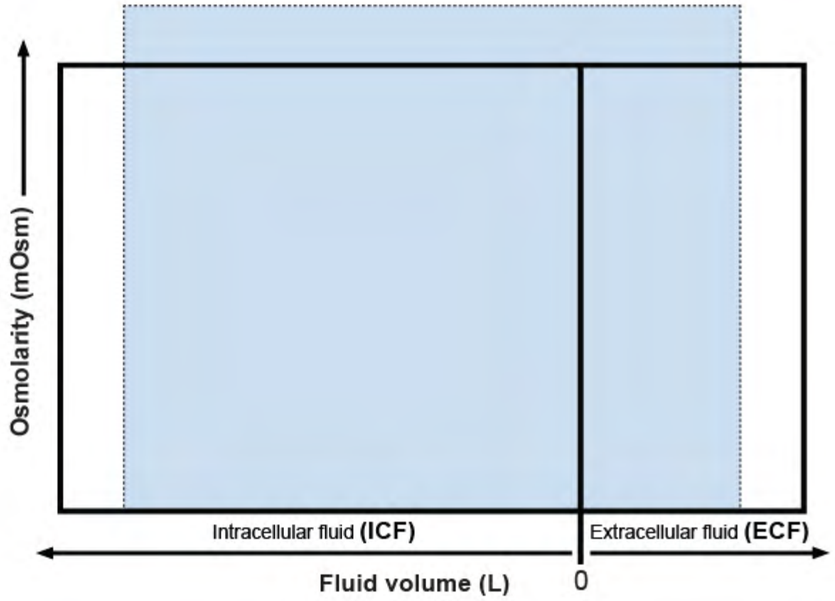
©UWorld

Which of the following conditions is most likely to cause the findings shown in the image?

- A. Acute gastrointestinal hemorrhage
- B. Adrenal insufficiency
- C. Diabetes insipidus
- D. Hypertonic saline infusion
- E. Primary polydipsia

Submit

https://t.me/USMLEWorldStep1



©UWorld

Which of the following conditions is most likely to cause the findings shown in the image?

- A. Acute gastrointestinal hemorrhage (17%)
- B. Adrenal insufficiency (7%)
- ✓ C. Diabetes insipidus (55%)
- D. Hypertonic saline infusion (14%)
- E. Primary polydipsia (3%)

Correct

55% Answered correctly

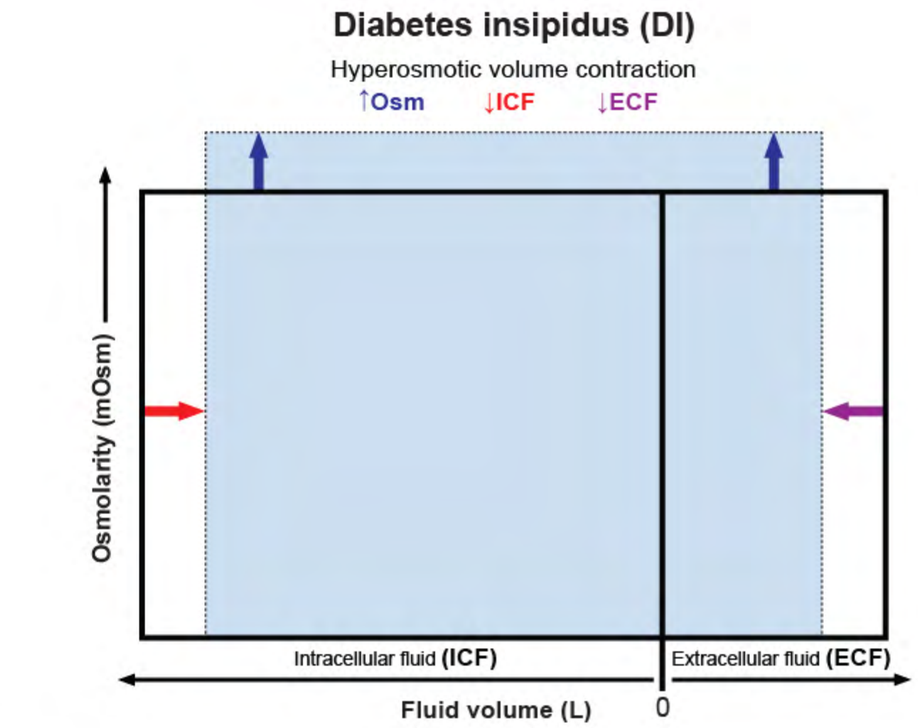
11 secs Time Spent

2023 Version

https://t.me/USMLEWorldStep1

Explanation

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

The fig
osmol

This p
damag
kidney
the los
compartments. Hyperosmotic volume contraction can occur in the setting of diabetes insipidus, decreased fluid intake (dehydration), and with profuse sweating (due to the hypotonic nature of sweat).

https://t.me/USMLEWorldStep1

©UWorld

The figure shows the volume of the intracellular (ICF) and extracellular (ECF) fluid compartments (x-axis) and the osmolarity of the fluid in those compartments (y-axis).

This patient's recent **head trauma** is consistent with **central diabetes insipidus** due to hypothalamic/pituitary damage. The resulting decrease in vasopressin secretion leads to **excessive free water excretion** by the kidneys, causing **hyperosmotic volume contraction**. This condition occurs when the loss of free water exceeds the loss of electrolytes, resulting in **increased osmolarity** and **contracted volumes** in both the **ICF and ECF** compartments. Hyperosmotic volume contraction can occur in the setting of diabetes insipidus, decreased fluid intake (dehydration), and with profuse sweating (due to the hypotonic nature of sweat).

(Choice A) Acute gastrointestinal hemorrhage (or diarrhea) would cause an isotonic loss of ECF volume, with no effects on osmolarity or ICF volume. This is referred to as isosmotic volume contraction.

(Choice B) The lack of aldosterone in adrenal insufficiency causes loss of NaCl with ECF volume depletion (hyposmotic volume contraction). The low osmolarity of the ECF results in shifting of free water into the ICF compartment, causing ICF expansion.

(Choice D) Infusion of large amounts of hypertonic saline leads to hypertonic volume expansion. Both the volume and osmolarity of the ECF are increased. The high osmolarity of the ECF leads to shifting of water from the ICF, further increasing the ECF volume.

(Choice E) Primary polydipsia (excessive water consumption) and SIADH (inappropriately high vasopressin levels) both cause retention of free water in the body. This leads to expansion of the ICF compartment and a decrease in the osmolarity of both compartments (hyposmotic volume expansion). Expansion of the ECF compartment is limited in these conditions due to compensatory secretion of aldosterone and natriuretic peptides, which help to normalize the extracellular fluid volume. Thus, affected patients are clinically euvolemic.

Educational objective:
Volume contraction and expansion can be divided into isosmotic, hyposmotic, and hyperosmotic states. Hyperosmotic volume contraction is caused by a loss of free water (with retention of electrolytes). It can occur in patients with diabetes insipidus or as a result of decreased fluid intake/excessive sweating.

https://t.me/USMLEWorldStep1

©UWorld

The figure shows the volume of the intracellular (ICF) and extracellular (ECF) fluid compartments (x-axis) and the osmol

This p
damag
kidney
the los
compa
intake

(Choi
effects

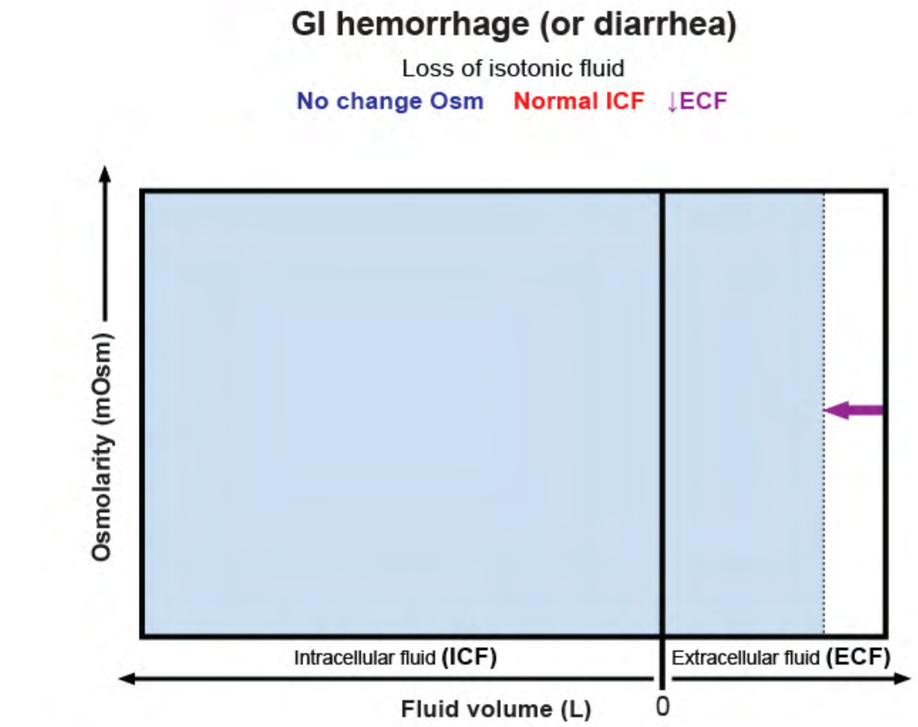
(Choi
(hypos
compa

(Choi
and os
further

(Choi
levels)
decrea
compa
which

Educa
Volum
Hyper
patients with diabetes insipidus or as a result of decreased fluid intake/excessive sweating.

Exhibit Display



©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

©UWorld

The figure shows the volume of the intracellular (ICF) and extracellular (ECF) fluid compartments (x-axis) and the osmol

This p
damag
kidney
the los
compa
intake

(Choi
effects

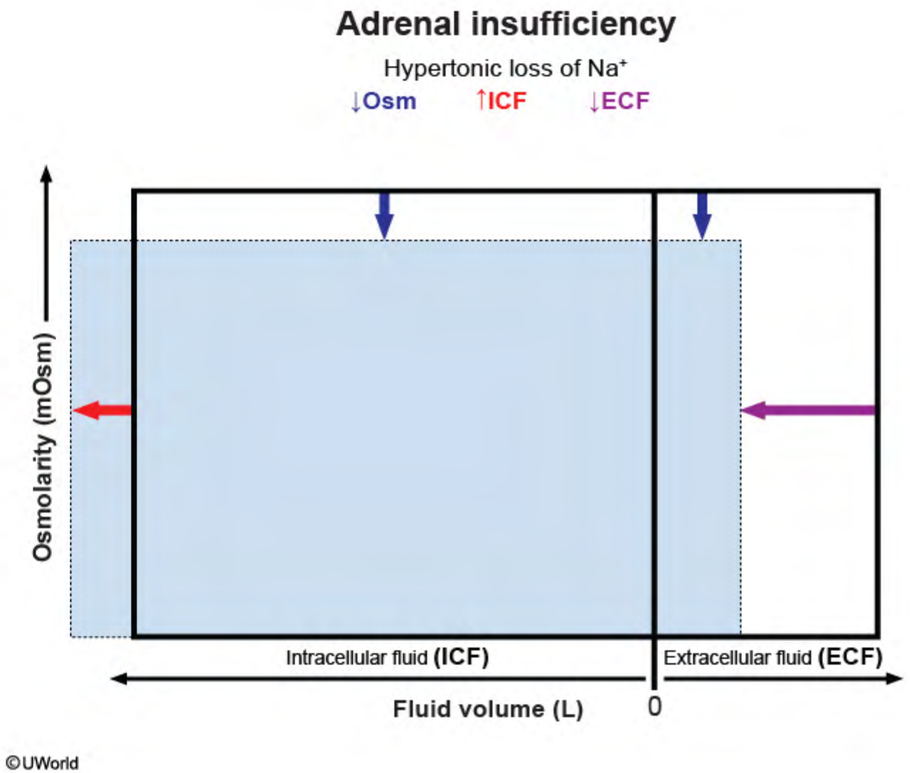
(Choi
(hypos
compa

(Choi
and os
further

(Choi
levels)
decrea
compa
which

Educa
Volum
Hyper
patients with diabetes insipidus or as a result of decreased fluid intake/excessive sweating.

Exhibit Display



©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

©UWorld

The figure shows the volume of the intracellular (ICF) and extracellular (ECF) fluid compartments (x-axis) and the osmol

This p
damag
kidney
the los
compa
intake

(Choi
effects

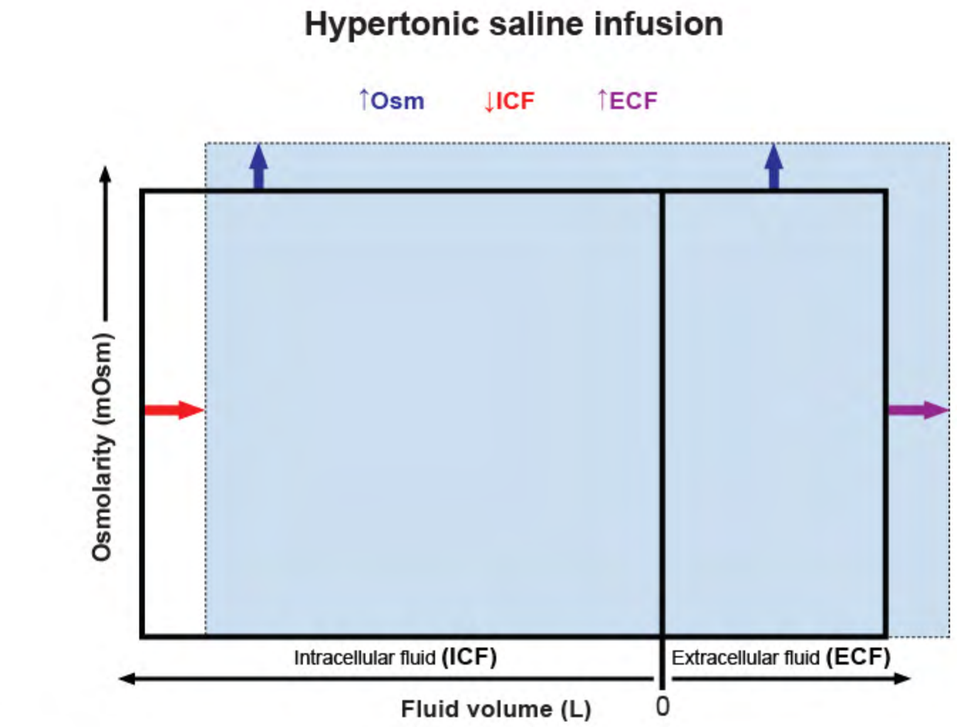
(Choi
(hypos
compa

(Choi
and os
further

(Choi
levels)
decrea
compa
which

Educa
Volum
Hyper
patients with diabetes insipidus or as a result of decreased fluid intake/excessive sweating.

Exhibit Display



©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

©UWorld

The figure shows the volume of the intracellular (ICF) and extracellular (ECF) fluid compartments (x-axis) and the osmol

This p
damag
kidney
the los
compa
intake

(Choi
effects

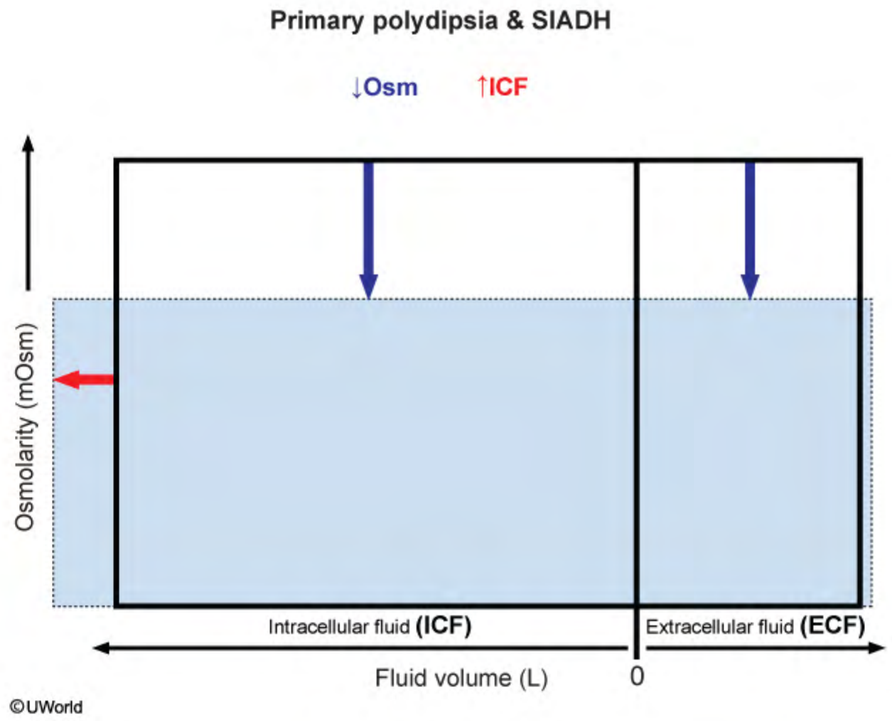
(Choi
(hypos
compa

(Choi
and os
further

(Choi
levels)
decrea
compa
which

Educa
Volum
Hyper
patients with diabetes insipidus or as a result of decreased fluid intake/excessive sweating.

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

A 34-year-old man comes to the office with his girlfriend for follow-up of type 1 diabetes mellitus. He was diagnosed 15 years ago and is currently treated with a combination of basal and rapid-acting insulin injections. The patient has been experiencing intermittent episodes of hypoglycemia with a blood glucose of 35-54 mg/dL. Two weeks ago, he was taken to the emergency department after passing out due to low glucose levels. The patient is prescribed an injectable medication to be administered at home by a caregiver when hypoglycemia is associated with impaired consciousness. This medication rapidly improves hypoglycemia by which of the following mechanisms?

- A. Decreasing uptake of glucose by fat and muscles
- B. Decreasing uptake of glucose by the liver
- C. Increasing gastrointestinal absorption of glucose
- D. Increasing gluconeogenesis
- E. Increasing glycogenolysis

Submit

https://t.me/USMLEWorldStep1

A 34-year-old man comes to the office with his girlfriend for follow-up of type 1 diabetes mellitus. He was diagnosed 15 years ago and is currently treated with a combination of basal and rapid-acting insulin injections. The patient has been experiencing intermittent episodes of hypoglycemia with a blood glucose of 35-54 mg/dL. Two weeks ago, he was taken to the emergency department after passing out due to low glucose levels. The patient is prescribed an injectable medication to be administered at home by a caregiver when hypoglycemia is associated with impaired consciousness. This medication rapidly improves hypoglycemia by which of the following mechanisms?

- ✗ A. Decreasing uptake of glucose by fat and muscles (10%)
- B. Decreasing uptake of glucose by the liver (6%)
- C. Increasing gastrointestinal absorption of glucose (3%)
- D. Increasing gluconeogenesis (34%)
- ✓ E. Increasing glycogenolysis (46%)

Incorrect
Correct answer
E

46%
Answered correctly

04 secs
Time Spent

2023
Version

Explanation

Metabolic effects of glucagon	
Liver	• ↑ glycogenolysis (primary) • ↑ gluconeogenesis, ↓ glycolysis (secondary) • ↓ lipogenesis
Adipose	• ↑ lipolysis
Heart	• ↑ heart rate, contractility (high dose)

https://t.me/USMLEWorldStep1

Metabolic effects of glucagon	
Liver	• ↑ glycogenolysis (primary) • ↑ gluconeogenesis, ↓ glycolysis (secondary) • ↓ lipogenesis
Adipose	• ↑ lipolysis
Heart	• ↑ heart rate, contractility (high dose) • Useful in treating beta blocker overdose

Hypoglycemia initially manifests with neurogenic (autonomic) symptoms, including anxiety, tremor, and sweating. However, as hypoglycemia worsens patients may develop life-threatening neuroglycopenic symptoms, including confusion, **loss of consciousness**, and seizures. Mild to moderate hypoglycemia is usually self-treated with oral fast-acting carbohydrates (eg, glucose tablets, fruit juices). However, when hypoglycemia becomes severe enough to induce unconsciousness, **parenteral treatment** is necessary.

In a medical setting, severe hypoglycemia is usually treated with an infusion of glucose, but this requires intravenous access. In a nonmedical setting, severe hypoglycemia can be treated with **emergency glucagon kits**, which are produced in intranasal and subcutaneous/intramuscular formulations and can be administered by a caregiver or informed bystander.

Glucagon rapidly corrects hypoglycemia by **increasing hepatic glycogenolysis**; the free glucose residues are then released into the blood, causing a return to consciousness within 10-15 minutes of administration. Subsequently, glucagon induces gluconeogenesis and suppresses hepatic glucose uptake, which provide a delayed but somewhat more sustained effect **(Choices B and D)**.

(Choice A) Glucagon has little direct effect on glucose uptake in adipose and muscle tissue, which is primarily regulated by insulin. Although epinephrine raises blood glucose (in part) by suppression of peripheral glucose uptake and can be administered by auto-injector, it is less effective than glucagon for hypoglycemia and is primarily used for severe allergy/anaphylaxis.

https://t.me/USMLEWorldStep1

Hypoglycemia initially manifests with neurogenic (autonomic) symptoms, including anxiety, tremor, and sweating. However, as hypoglycemia worsens patients may develop life-threatening neuroglycopenic symptoms, including confusion, **loss of consciousness**, and seizures. Mild to moderate hypoglycemia is usually self-treated with oral fast-acting carbohydrates (eg, glucose tablets, fruit juices). However, when hypoglycemia becomes severe enough to induce unconsciousness, **parenteral treatment** is necessary.

In a medical setting, severe hypoglycemia is usually treated with an infusion of glucose, but this requires intravenous access. In a nonmedical setting, severe hypoglycemia can be treated with **emergency glucagon kits**, which are produced in intranasal and subcutaneous/intramuscular formulations and can be administered by a caregiver or informed bystander.

Glucagon rapidly corrects hypoglycemia by **increasing hepatic glycogenolysis**; the free glucose residues are then released into the blood, causing a return to consciousness within 10-15 minutes of administration. Subsequently, glucagon induces gluconeogenesis and suppresses hepatic glucose uptake, which provide a delayed but somewhat more sustained effect **(Choices B and D)**.

(Choice A) Glucagon has little direct effect on glucose uptake in adipose and muscle tissue, which is primarily regulated by insulin. Although epinephrine raises blood glucose (in part) by suppression of peripheral glucose uptake and can be administered by auto-injector, it is less effective than glucagon for hypoglycemia and is primarily used for severe allergy/anaphylaxis.

(Choice C) Glucose is taken up from the intestinal lumen into epithelial cells via sodium-glucose cotransporter-1 (SGLT-1) and then passed into the blood via glucose transporter 2 (GLUT-2). Glucagon causes a decrease in intestinal motility but does not have a major effect on the transport of glucose by SGLT-1 or GLUT-2.

Educational objective:
Severe hypoglycemia causing impaired conciousness can be treated by a caregiver or bystander with injectable or intranasal glucagon. Glucagon rapidly corrects hypoglycemia by increasing hepatic glycogenolysis, resulting in the release of glucose from preexisting hepatic glycogen stores.

References

- Novel preparations of glucagon for the prevention and treatment of hypoglycemia.

https://t.me/USMLEWorldStep1

A 54-year-old man comes to the office due to worsening fatigue, generalized weakness, and an unintentional 7-kg (15.4-lb) weight loss over the past several weeks. The patient has no prior medical conditions and takes no medications. He has a 40-pack-year history of smoking and does not use alcohol or illicit drugs. Blood pressure is 160/100 mm Hg and pulse is 80/min. Physical examination shows darkening of the skin in sun-exposed areas. There are scattered ecchymoses on the extremities. Mild proximal muscle weakness is present. Chest imaging reveals a 6-cm, irregular right lung mass with mediastinal lymphadenopathy. Which of the following is most likely responsible for the patient's current symptoms?

- A. ACTH production from an ectopic site
- B. Excess cortisol release from the lung mass
- C. Excessive ACTH secretion from the pituitary
- D. Hypothalamic dysfunction from metastatic process
- E. Malignant invasion of the adrenal cortex

Submit

https://t.me/USMLEWorldStep1

A 54-year-old man comes to the office due to worsening fatigue, generalized weakness, and an unintentional 7-kg (15.4-lb) weight loss over the past several weeks. The patient has no prior medical conditions and takes no medications. He has a 40-pack-year history of smoking and does not use alcohol or illicit drugs. Blood pressure is 160/100 mm Hg and pulse is 80/min. Physical examination shows darkening of the skin in sun-exposed areas. There are scattered ecchymoses on the extremities. Mild proximal muscle weakness is present. Chest imaging reveals a 6-cm, irregular right lung mass with mediastinal lymphadenopathy. Which of the following is most likely responsible for the patient's current symptoms?

- ✓ A. ACTH production from an ectopic site (85%)
- ✗ B. Excess cortisol release from the lung mass (3%)
- C. Excessive ACTH secretion from the pituitary (3%)
- D. Hypothalamic dysfunction from metastatic process (2%)
- E. Malignant invasion of the adrenal cortex (4%)

Incorrect
Correct answer
A

85%
Answered correctly

04 secs
Time Spent

2023
Version

Explanation

Common paraneoplastic syndromes associated with lung cancer	
Endocrine	• Syndrome of inappropriate antidiuretic hormone* • Parathyroid hormone-related protein secretion (hypercalcemia) • Ectopic ACTH production (Cushing syndrome)*
Neurologic	• Lambert-Eaton myasthenic syndrome* • Paraneoplastic cerebellar degeneration*

https://t.me/USMLEWorldStep1

Common paraneoplastic syndromes associated with lung cancer	
Endocrine	• Syndrome of inappropriate antidiuretic hormone* • Parathyroid hormone-related protein secretion (hypercalcemia) • Ectopic ACTH production (Cushing syndrome)*
Neurologic	• Lambert-Eaton myasthenic syndrome* • Paraneoplastic cerebellar degeneration*
Musculoskeletal	• Hypertrophic osteoarthropathy (clubbing)
*Generally associated with small cell lung cancer.	

This patient has fatigue, weakness, and weight loss associated with a suspicious **lung mass**. His hypertension, ecchymoses, and hyperpigmentation suggest **paraneoplastic hypercortisolism** (Cushing syndrome) due to **ectopic ACTH** secretion. As with primary adrenal insufficiency, excess ACTH secretion leads to hyperpigmentation, likely due to co-secretion of alpha-melanocyte-stimulating hormone (alpha-MSH) (both ACTH and alpha-MSH are derived from pro-opiomelanocortin) and direct stimulation of the MC2R receptor on melanocytes by ACTH. Although patients with paraneoplastic hypercortisolism may have many of the typical metabolic features of cortisol excess (eg, hypertension, hyperglycemia, edema), **weight loss** is more common than classic Cushingoid central obesity.

Paraneoplastic hypercortisolism is most commonly associated with small cell lung cancer but can also be seen with other neuroendocrine tumors (eg, bronchial or pancreatic carcinoid). ACTH secreted by small cell lung cancer is not inhibited by high-dose exogenous corticosteroids (eg, dexamethasone), whereas pituitary ACTH secretion decreases via negative feedback.

(Choice B) Cortisol is produced by the zona fasciculata of the adrenal cortex, and autonomous cortisol production (ie, ACTH-independent hypercortisolism) is almost always due to a primary adrenal disorder (eg, adrenal adenoma). Regardless of the source, excess cortisol in a patient with intact hypothalamus-pituitary function suppresses ACTH and patients do not develop hyperpigmentation.

https://t.me/USMLEWorldStep1

and alpha-MSH are derived from pro-opiomelanocortin) and direct stimulation of the MC2R receptor on melanocytes by ACTH. Although patients with paraneoplastic hypercortisolism may have many of the typical metabolic features of cortisol excess (eg, hypertension, hyperglycemia, edema), **weight loss** is more common than classic Cushingoid central obesity.

Paraneoplastic hypercortisolism is most commonly associated with small cell lung cancer but can also be seen with other neuroendocrine tumors (eg, bronchial or pancreatic carcinoid). ACTH secreted by small cell lung cancer is not inhibited by high-dose exogenous corticosteroids (eg, dexamethasone), whereas pituitary ACTH secretion decreases via negative feedback.

(Choice B) Cortisol is produced by the zona fasciculata of the adrenal cortex, and autonomous cortisol production (ie, ACTH-independent hypercortisolism) is almost always due to a primary adrenal disorder (eg, adrenal adenoma). Regardless of the source, excess cortisol in a patient with intact hypothalamus-pituitary function suppresses ACTH and patients do not develop hyperpigmentation.

(Choice C) Given this patient's large lung mass and associated weight loss (instead of weight gain and central fat deposition), paraneoplastic ACTH secretion is more likely than an ACTH-producing pituitary adenoma (Cushing disease).

(Choice D) Metastasis to the hypothalamus would likely cause endocrine insufficiency resulting from a lack of trophic hormones to the anterior pituitary. Decreased production of corticotropin-releasing hormone would lead to central adrenal insufficiency, not hypercortisolism.

(Choice E) The adrenal glands are a common site of metastasis. If significant destruction of the adrenal cortical tissue occurs bilaterally, adrenal insufficiency may result. A subsequent increase of ACTH may cause hyperpigmentation; however, symptoms of adrenal insufficiency (eg, hypotension) would be expected, as opposed to the symptoms of cortisol excess seen in this patient.

Educational objective:
Paraneoplastic hypercortisolism, most commonly caused by small cell lung cancer, is due to ectopic ACTH secretion. Clinical features include hypertension, hyperglycemia, edema, and hyperpigmentation. Unlike nonparaneoplastic Cushing syndrome, central obesity is uncommon.

https://t.me/USMLEWorldStep1

Common paraneoplastic syndromes associated with lung cancer

	Syndrome of inappropriate antidiuretic hormone*

Exhibit Display

Clinical features of Cushing syndrome
• **Central obesity** (eg, fat accumulation in the face [ie, moon face] & back of the neck [ie, buffalo hump]) • **Glucose intolerance** • Hypertension • Menstrual changes & decreased libido • Skin atrophy • Easy bruisability • Hirsutism & acne (excess androgens) • Proximal muscle weakness

New | Existing | My Notebook

This p
ecchy
ectopi
hyperp
and al
melan
metab
than c

Paran
other r
not inh
decrea

(Choi
(ie, AC
adeno
suppre

(Choice C) Given this patient's large lung mass and associated weight loss (instead of weight gain and central fat deposition), paraneoplastic ACTH secretion is more likely than an ACTH-producing pituitary adenoma (Cushing

https://t.me/USMLEWorldStep1

Researchers are studying factors contributing to higher morbidity and mortality in infants born prematurely. They find that, compared to term infants, preterm infants have a lesser amount of specialized connective tissue found in the supraclavicular area and around major blood vessels and abdominal organs. These highly vascular tissues are composed of cells containing multiple lipid droplets and abundant mitochondria. Which of the following processes is most likely to be impaired in the preterm infants lacking these tissues?

- A. Collagen synthesis
- B. Gluconeogenesis
- C. Glycogen storage
- D. Ketone body production
- E. Thermogenesis

Submit

https://t.me/USMLEWorldStep1

Researchers are studying factors contributing to higher morbidity and mortality in infants born prematurely. They find that, compared to term infants, preterm infants have a lesser amount of specialized connective tissue found in the supraclavicular area and around major blood vessels and abdominal organs. These highly vascular tissues are composed of cells containing multiple lipid droplets and abundant mitochondria. Which of the following processes is most likely to be impaired in the preterm infants lacking these tissues?

- ✗ A. Collagen synthesis (7%)
- B. Gluconeogenesis (6%)
- C. Glycogen storage (5%)
- D. Ketone body production (7%)
- ✓ E. Thermogenesis (72%)

Incorrect
Correct answer
E

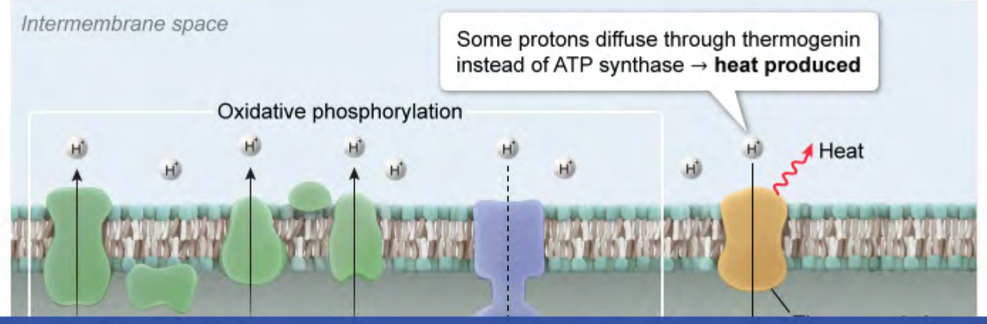
72%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

Uncoupling of oxidative phosphorylation by thermogenin

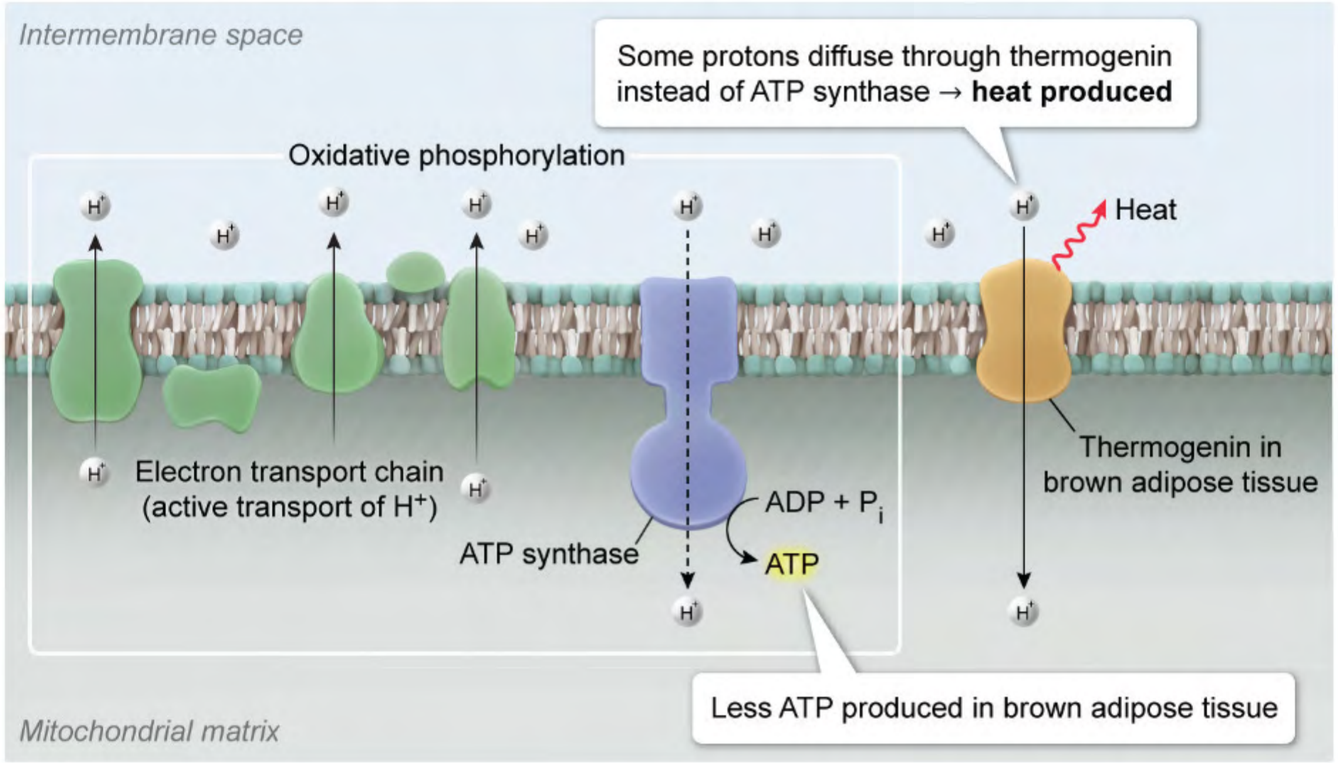


https://t.me/USMLEWorldStep1

Researchers are studying factors contributing to higher morbidity and mortality in infants born prematurely. They find th
the su
compo
is mos

Exhibit Display

Uncoupling of oxidative phosphorylation by thermogenin



©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

Neonates are highly susceptible to **hypothermia** due to an immature nervous system (impaired thermoregulation), a high body surface area to volume ratio (increased relative heat loss), and a decreased ability to shiver (impaired heat generation). To improve their tolerance to colder temperatures, newborns have significant amounts of **brown adipose** tissue, which produces heat, in the **supraclavicular area** and around major blood vessels and abdominal organs. However, **preterm infants** have less brown adipose tissue than full-term infants and subsequently have **impaired thermogenesis** and an increased risk of hypothermia.

Unlike white adipocytes that contain one intracytoplasmic fat droplet, brown adipocytes possess several small intracytoplasmic lipid droplets and **abundant mitochondria** (which give these cells a tan color). Because of its extensive metabolic activity, brown adipose tissue also has a higher oxygen requirement and contains more capillaries than white adipose tissue.

In most human cells, mitochondria are the major site of ATP production. However, in the mitochondria of brown adipose tissue, electron transport and oxidative phosphorylation are **uncoupled** by the presence of **thermogenin** (also known as uncoupling protein-1) in the inner mitochondrial membrane. Thermogenin is a carrier protein that allows protons pumped out of the mitochondrial matrix to leak back into the matrix without triggering synthesis of ATP. This allows for a **larger proportion** of the energy released by electron transport to be **dissipated as heat**.

(Choice A) Collagen is synthesized by fibroblasts, which do not contain intracellular lipid droplets or abundant mitochondria. In addition, collagenous connective tissue is often poorly vascularized. Synthesis of collagen is not impaired in preterm infants.

(Choices B and D) During the fasting state, white adipose tissue releases triglycerides that are used for gluconeogenesis (glycerin) and ketone body formation (fatty acids). Although it is found in lesser amounts in preterm infants, white adipose tissue is poorly vascularized, and its cells contain only one intracytoplasmic fat vacuole and have a lower concentration of mitochondria compared to brown adipose cells.

(Choice C) Preterm infants are at risk for hypoglycemia due to decreased glycogen stores in the liver, not as a result of less brown adipose tissue.

Educational objective:
Brown adipose cells, which contain multiple lipid droplets and abundant mitochondria, produce large amounts of heat (ie, thermogenesis) by uncoupling oxidative phosphorylation with the protein thermogenin. Preterm infants

https://t.me/USMLEWorldStep1

adipose tissue, which produces heat, in the **supraclavicular area** and around major blood vessels and abdominal organs. However, **preterm infants** have less brown adipose tissue than full-term infants and subsequently have **impaired thermogenesis** and an increased risk of hypothermia.

Unlike white adipocytes that contain one intracytoplasmic fat droplet, brown adipocytes possess several small intracytoplasmic lipid droplets and **abundant mitochondria** (which give these cells a tan color). Because of its extensive metabolic activity, brown adipose tissue also has a higher oxygen requirement and contains more capillaries than white adipose tissue.

In most human cells, mitochondria are the major site of ATP production. However, in the mitochondria of brown adipose tissue, electron transport and oxidative phosphorylation are **uncoupled** by the presence of **thermogenin** (also known as uncoupling protein-1) in the inner mitochondrial membrane. Thermogenin is a carrier protein that allows protons pumped out of the mitochondrial matrix to leak back into the matrix without triggering synthesis of ATP. This allows for a **larger proportion** of the energy released by electron transport to be **dissipated as heat**.

(Choice A) Collagen is synthesized by fibroblasts, which do not contain intracellular lipid droplets or abundant mitochondria. In addition, collagenous connective tissue is often poorly vascularized. Synthesis of collagen is not impaired in preterm infants.

(Choices B and D) During the fasting state, white adipose tissue releases triglycerides that are used for gluconeogenesis (glycerin) and ketone body formation (fatty acids). Although it is found in lesser amounts in preterm infants, white adipose tissue is poorly vascularized, and its cells contain only one intracytoplasmic fat vacuole and have a lower concentration of mitochondria compared to brown adipose cells.

(Choice C) Preterm infants are at risk for hypoglycemia due to decreased glycogen stores in the liver, not as a result of less brown adipose tissue.

Educational objective:
Brown adipose cells, which contain multiple lipid droplets and abundant mitochondria, produce large amounts of heat (ie, thermogenesis) by uncoupling oxidative phosphorylation with the protein thermogenin. Preterm infants are at increased risk for hypothermia because they have less brown adipose tissue than term infants.

References

- Relevance of brown adipose tissue in infancy and adolescence

https://t.me/USMLEWorldStep1

A 55-year-old woman, gravida 3 para 3, comes to the office due to constipation. For the past 6 months, the patient has had increasing constipation associated with mild, crampy abdominal pain and fatigue. She has only 1 or 2 bowel movements every week. Medical history is notable for nephrolithiasis, for which the patient was briefly hospitalized a year ago. She has not undergone colonoscopy. Vital signs are normal. The abdomen is soft. Rectal tone is normal. Deep tendon reflexes are 2+. The remainder of the examination shows no abnormalities. Laboratory results are as follows:

Serum chemistry

Sodium	140 mEq/L
Potassium	3.9 mEq/L
Creatinine	0.9 mg/dL
Calcium	11.5 mg/dL
Phosphorus (inorganic)	2.2 mg/dL

Which of the following is the most likely underlying cause of constipation in this patient?

- A. Decreased colonic smooth muscle contractility
- B. Dysfunction of pelvic floor muscles
- C. Impaired sacral parasympathetic innervation
- D. Malignant obstruction of colon
- E. Segmental demyelination of autonomic nerves

Submit

https://t.me/USMLEWorldStep1

A 55-year-old woman, gravida 3 para 3, comes to the office due to constipation. For the past 6 months, the patient has had increasing constipation associated with mild, crampy abdominal pain and fatigue. She has only 1 or 2 bowel movements every week. Medical history is notable for nephrolithiasis, for which the patient was briefly hospitalized a year ago. She has not undergone colonoscopy. Vital signs are normal. The abdomen is soft. Rectal tone is normal. Deep tendon reflexes are 2+. The remainder of the examination shows no abnormalities. Laboratory results are as follows:

Serum chemistry

Sodium	140 mEq/L
Potassium	3.9 mEq/L
Creatinine	0.9 mg/dL
Calcium	11.5 mg/dL
Phosphorus (inorganic)	2.2 mg/dL

Which of the following is the most likely underlying cause of constipation in this patient?

- ✓ A. Decreased colonic smooth muscle contractility (68%)
- B. Dysfunction of pelvic floor muscles (6%)
- C. Impaired sacral parasympathetic innervation (8%)
- D. Malignant obstruction of colon (13%)
- E. Segmental demyelination of autonomic nerves (2%)

Correct

68% Answered correctly

04 secs Time Spent

2023 Version

Explanation

https://t.me/USMLEWorldStep1

Hypercalcemia-induced constipation	
Significant causes	• Primary hyperparathyroidism • Hypercalcemia of malignancy • Vitamin D toxicity, milk-alkali syndrome
Typical symptoms	• Decreased frequency/increased hardness of stools • Nausea, abdominal pain • Nongastrointestinal symptoms: fatigue, polyuria, neuropsychiatric disturbance
Pathophysiology	• Inhibition of smooth muscle depolarization • Decreased intestinal contractility/motility

This patient has **constipation** associated with **hypercalcemia** and hypophosphatemia, which is a common presentation of **primary hyperparathyroidism** (PHPT). PHPT is usually caused by a benign parathyroid adenoma that autonomously secretes parathyroid hormone (PTH), leading to increased bone resorption, increased renal calcium reabsorption, and increased intestinal calcium absorption (due to increased production of 1,25-dihydroxyvitamin D). This patient's history of **renal stones** also indicates hyperparathyroidism and is due to increased urinary calcium excretion despite maximal renal tubular calcium reabsorption.

Hypercalcemia **inhibits nerve depolarization** by interfering with sodium movement through voltage-gated sodium channels, leading to **impaired smooth muscle contraction** and **reduced colonic motility**. Symptoms include constipation, crampy abdominal pain, and nausea. Other potential gastrointestinal manifestations of hypercalcemia include acute pancreatitis (due to increased conversion of trypsinogen to trypsin) and peptic ulcer (due to increased release of gastrin).

(Choice B) Dyssynergic defecation is characterized by altered passage of stool through the anorectum due to uncoordinated contraction and relaxation of pelvic floor muscles. It is often caused by obstetric complications during vaginal delivery. However, hypercalcemia and hypophosphatemia would not be present, and most patients have either anal sphincter dysfunction or the absence of perianal descent (this patient's rectal tone is normal).

(Choices C and E) Intestinal motor function is generally stimulated by the parasympathetic nervous system and inhibited by the sympathetic nervous system. Although constipation can occur due to autonomic dysfunction from

https://t.me/USMLEWorldStep1

This patient has **constipation** associated with **hypercalcemia** and hypophosphatemia, which is a common presentation of **primary hyperparathyroidism** (PHPT). PHPT is usually caused by a benign parathyroid adenoma that autonomously secretes parathyroid hormone (PTH), leading to increased bone resorption, increased renal calcium reabsorption, and increased intestinal calcium absorption (due to increased production of 1,25-dihydroxyvitamin D). This patient's history of **renal stones** also indicates hyperparathyroidism and is due to increased urinary calcium excretion despite maximal renal tubular calcium reabsorption.

Hypercalcemia **inhibits nerve depolarization** by interfering with sodium movement through voltage-gated sodium channels, leading to **impaired smooth muscle contraction** and **reduced colonic motility**. Symptoms include constipation, crampy abdominal pain, and nausea. Other potential gastrointestinal manifestations of hypercalcemia include acute pancreatitis (due to increased conversion of trypsinogen to trypsin) and peptic ulcer (due to increased release of gastrin).

(Choice B) Dyssynergic defecation is characterized by altered passage of stool through the anorectum due to uncoordinated contraction and relaxation of pelvic floor muscles. It is often caused by obstetric complications during vaginal delivery. However, hypercalcemia and hypophosphatemia would not be present, and most patients have either anal sphincter dysfunction or the absence of perianal descent (this patient's rectal tone is normal).

(Choices C and E) Intestinal motor function is generally stimulated by the parasympathetic nervous system and inhibited by the sympathetic nervous system. Although constipation can occur due to autonomic dysfunction from demyelination (eg, multiple sclerosis) or nerve fiber interruption (eg, traumatic spinal cord injury), these disorders would not explain this patient's electrolyte abnormalities.

(Choice D) Colon cancer can cause intestinal obstruction, which can interfere with the passage of stool, and can be associated with hypercalcemia (bone metastasis); however, this would result in PTH suppression, so it is unlikely to cause hypophosphatemia. This patient's history of renal stones also is more consistent with primary hyperparathyroidism.

Educational objective:
Hypercalcemia inhibits nerve depolarization, leading to impaired smooth muscle contraction and reduced colonic motility. Symptoms include constipation, crampy abdominal pain, and nausea.

https://t.me/USMLEWorldStep1

A 35-year-old woman is evaluated for a 3-month history of appetite loss, fatigue, weight loss, and abdominal pain. She has no chronic medical conditions and takes no medications. While undergoing upper gastrointestinal endoscopy, the patient develops cardiovascular collapse and dies, despite aggressive resuscitative measures. On autopsy, increased pigmentation is noted around the nipple areola and anal and vaginal mucous membranes. Which of the following additional findings are most likely to be seen on autopsy?

- A. Atrophy of both adrenal glands
- B. Bilateral adrenal hemorrhage
- C. Ischemic anterior pituitary necrosis
- D. Large pituitary tumor with hemorrhage
- E. Unilateral adrenal mass with contralateral adrenal atrophy

Submit

https://t.me/USMLEWorldStep1

A 35-year-old woman is evaluated for a 3-month history of appetite loss, fatigue, weight loss, and abdominal pain. She has no chronic medical conditions and takes no medications. While undergoing upper gastrointestinal endoscopy, the patient develops cardiovascular collapse and dies, despite aggressive resuscitative measures. On autopsy, increased pigmentation is noted around the nipple areola and anal and vaginal mucous membranes. Which of the following additional findings are most likely to be seen on autopsy?

- ✓ A. Atrophy of both adrenal glands (52%)
- ✗ B. Bilateral adrenal hemorrhage (18%)
- C. Ischemic anterior pituitary necrosis (4%)
- D. Large pituitary tumor with hemorrhage (12%)
- E. Unilateral adrenal mass with contralateral adrenal atrophy (12%)

Incorrect
Correct answer
A

52%
Answered correctly

04 secs
Time Spent

2023
Version

Explanation

Primary adrenal insufficiency	
Etiology	• **Autoimmune adrenalitis** (most common) • Infection (eg, tuberculosis) • Hemorrhagic infarction
Clinical features	• Fatigue, weakness, anorexia/weight loss • Nausea/vomiting/abdominal pain • Postural hypotension • Hyperpigmentation

https://t.me/USMLEWorldStep1

Explanation

Primary adrenal insufficiency	
Etiology	• **Autoimmune adrenalitis** (most common) • Infection (eg, tuberculosis) • Hemorrhagic infarction
Clinical features	• Fatigue, weakness, anorexia/weight loss • Nausea/vomiting/abdominal pain • Postural hypotension • Hyperpigmentation • **Acute adrenal crisis:** confusion, shock
Laboratory findings	• Hyponatremia, hyperkalemia • Low morning cortisol, high ACTH • Eosinophilia

This patient with a three month history of weight loss, abdominal pain, and fatigue developed cardiovascular collapse during a medical procedure (endoscopy), which suggests **chronic adrenal insufficiency** complicated by **acute adrenal crisis**. Severe physiologic stress (eg, infection, medical procedures) normally induces increased glucocorticoid production; however, patients with adrenal insufficiency are unable to increase production. Adrenal crisis (eg, hypotension, shock) is rapidly fatal if unrecognized.

Adrenal insufficiency can be caused by dysfunction of either the adrenal glands (primary) or pituitary (secondary). This patient's concomitant **skin hyperpigmentation** is highly suggestive of chronic **primary adrenal insufficiency** (PAI), as the resulting cortisol deficiency leads to increased ACTH secretion. ACTH is derived from proopiomelanocortin (POMC), the same prohormone from which melanocyte-stimulating hormone (MSH) is derived. Increased ACTH also leads to increased MSH secretion, which results in hyperpigmentation.

Autoimmune adrenalitis is the most common cause (>90%) of chronic PAI and occurs due to autoantibody

https://t.me/USMLEWorldStep1

This patient with a three month history of weight loss, abdominal pain, and fatigue developed cardiovascular collapse during a medical procedure (endoscopy), which suggests **chronic adrenal insufficiency** complicated by **acute adrenal crisis**. Severe physiologic stress (eg, infection, medical procedures) normally induces increased glucocorticoid production; however, patients with adrenal insufficiency are unable to increase production. Adrenal crisis (eg, hypotension, shock) is rapidly fatal if unrecognized.

Adrenal insufficiency can be caused by dysfunction of either the adrenal glands (primary) or pituitary (secondary). This patient's concomitant **skin hyperpigmentation** is highly suggestive of chronic **primary adrenal insufficiency** (PAI), as the resulting cortisol deficiency leads to increased ACTH secretion. ACTH is derived from proopiomelanocortin (POMC), the same prohormone from which melanocyte-stimulating hormone (MSH) is derived. Increased ACTH also leads to increased MSH secretion, which results in hyperpigmentation.

Autoimmune adrenalitis is the most common cause (>90%) of chronic PAI and occurs due to autoantibody formation, resulting in **atrophy of the bilateral adrenal glands**. It can occur as an isolated disorder or in association with other autoimmune syndromes (eg, hypothyroidism, vitiligo).

(Choice B) Bilateral adrenal hemorrhage (Waterhouse-Friderichsen syndrome [WFS]) can cause PAI and adrenal crisis but is typically seen *acutely* in the setting of bacterial sepsis (eg, *Neisseria meningitidis*). However, hyperpigmentation occurs in *chronic* adrenal insufficiency and therefore would not be expected with WFS.

(Choices C and D) Ischemic necrosis of the pituitary (Sheehan syndrome) most commonly occurs due to hypoperfusion of the enlarged pituitary gland during childbirth. Acute pituitary hemorrhage (pituitary apoplexy) typically occurs in patients with pituitary adenomas. These conditions can cause central (secondary) adrenal insufficiency; however, hyperpigmentation is not seen because ACTH levels are low, and POMC levels are not increased.

(Choice E) A cortisol-producing adrenal tumor can cause contralateral adrenal atrophy due to suppression of ACTH secretion; however, it would not be associated with hyperpigmentation and would manifest as hypercortisolism rather than adrenal insufficiency.

Educational objective:
Primary adrenal insufficiency (PAI) is characterized by weight loss, abdominal pain, fatigue, and hyperpigmentation. Physiologic stress in patients with PAI can trigger acute adrenal crisis (eg, fever, shock, mental

https://t.me/USMLEWorldStep1

glucocorticoid production; however, patients with adrenal insufficiency are unable to increase production. Adrenal crisis (eg, hypotension, shock) is rapidly fatal if unrecognized.

Adrenal insufficiency can be caused by dysfunction of either the adrenal glands (primary) or pituitary (secondary). This patient's concomitant **skin hyperpigmentation** is highly suggestive of chronic **primary adrenal insufficiency** (PAI), as the resulting cortisol deficiency leads to increased ACTH secretion. ACTH is derived from proopiomelanocortin (POMC), the same prohormone from which melanocyte-stimulating hormone (MSH) is derived. Increased ACTH also leads to increased MSH secretion, which results in hyperpigmentation.

Autoimmune adrenalitis is the most common cause (>90%) of chronic PAI and occurs due to autoantibody formation, resulting in **atrophy of the bilateral adrenal glands**. It can occur as an isolated disorder or in association with other autoimmune syndromes (eg, hypothyroidism, vitiligo).

(Choice B) Bilateral adrenal hemorrhage (Waterhouse-Friderichsen syndrome [WFS]) can cause PAI and adrenal crisis but is typically seen *acutely* in the setting of bacterial sepsis (eg, *Neisseria meningitidis*). However, hyperpigmentation occurs in *chronic* adrenal insufficiency and therefore would not be expected with WFS.

(Choices C and D) Ischemic necrosis of the pituitary (Sheehan syndrome) most commonly occurs due to hypoperfusion of the enlarged pituitary gland during childbirth. Acute pituitary hemorrhage (pituitary apoplexy) typically occurs in patients with pituitary adenomas. These conditions can cause central (secondary) adrenal insufficiency; however, hyperpigmentation is not seen because ACTH levels are low, and POMC levels are not increased.

(Choice E) A cortisol-producing adrenal tumor can cause contralateral adrenal atrophy due to suppression of ACTH secretion; however, it would not be associated with hyperpigmentation and would manifest as hypercortisolism rather than adrenal insufficiency.

Educational objective:
Primary adrenal insufficiency (PAI) is characterized by weight loss, abdominal pain, fatigue, and hyperpigmentation. Physiologic stress in patients with PAI can trigger acute adrenal crisis (eg, fever, shock, mental status changes). Autoimmune adrenalitis is the most common cause of PAI and leads to bilateral adrenal atrophy.

References

- Diagnosis and classification of Addison's disease (autoimmune adrenalitis).

https://t.me/USMLEWorldStep1

glucocorticoid production; however, patients with adrenal insufficiency are unable to increase production. Adrenal crisis (eg, hypotension, shock) is rapidly fatal if unrecognized.

Adren
This p
(PAI),
proopi
derive

Autoi
format
associ

(Choi
crisis b
hyperp

(Choi
hypop
typical
insuffi
increa

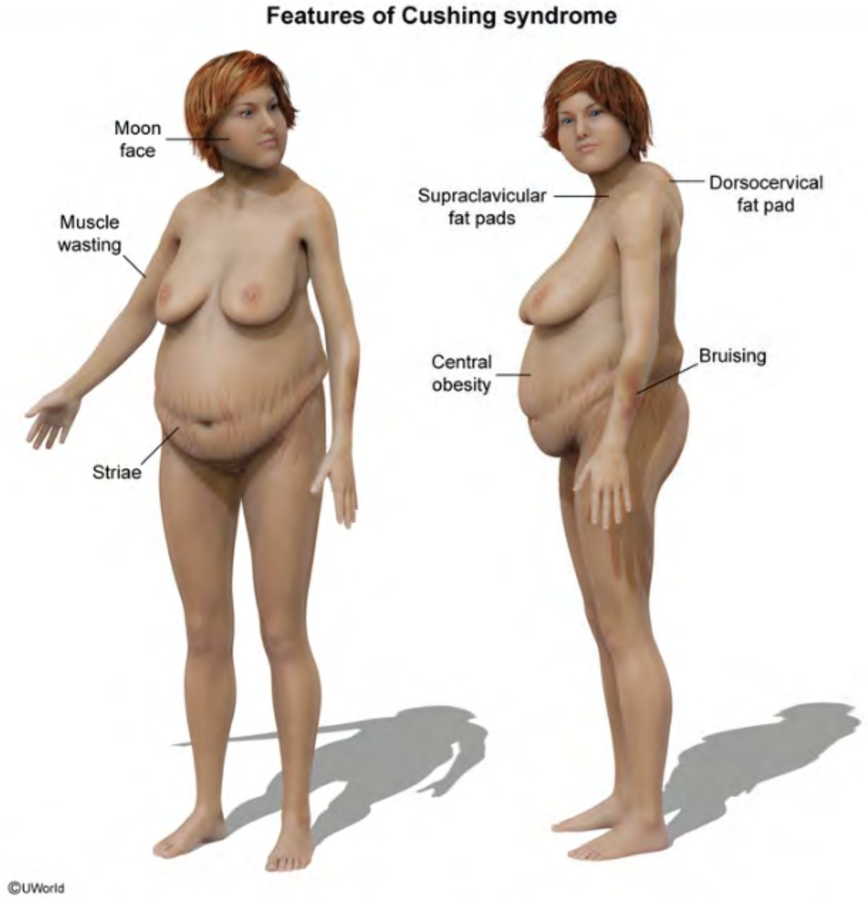
(Choi
ACTH
hyperc

Educa
Primar
hyperp
status

References

- Diagnosis and classification of Addison's disease (autoimmune adrenalitis).

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

A 22-year-old woman comes to the office due to palpitations, weight loss, and insomnia. She has lost 7 kg (15.4 lb) in the past 3 months. The patient has no other medical problems and takes no medication. She does not use tobacco, alcohol, or illicit drugs. Blood pressure is 130/80 mm Hg and pulse is 104/min and regular. The thyroid gland is diffusely enlarged and nontender on palpation. Laboratory studies show markedly decreased serum TSH and elevated thyroxine levels. Methimazole monotherapy is initiated. Two months later, her symptoms had resolved. The treatment most likely improved this patient's condition by directly inhibiting which of the following processes?

- A. Colloid production
- B. Coupling of iodotyrosines
- C. Iodide uptake by the thyroid gland
- D. Peripheral thyroxine to triiodothyronine conversion
- E. Triiodothyronine/thyroxine effect on target tissues

Submit

https://t.me/USMLEWorldStep1

A 22-year-old woman comes to the office due to palpitations, weight loss, and insomnia. She has lost 7 kg (15.4 lb) in the past 3 months. The patient has no other medical problems and takes no medication. She does not use tobacco, alcohol, or illicit drugs. Blood pressure is 130/80 mm Hg and pulse is 104/min and regular. The thyroid gland is diffusely enlarged and nontender on palpation. Laboratory studies show markedly decreased serum TSH and elevated thyroxine levels. Methimazole monotherapy is initiated. Two months later, her symptoms had resolved. The treatment most likely improved this patient's condition by directly inhibiting which of the following processes?

- ✗ A. Colloid production (1%)
- ✓ B. Coupling of iodotyrosines (74%)
- C. Iodide uptake by the thyroid gland (7%)
- D. Peripheral thyroxine to triiodothyronine conversion (14%)
- E. Triiodothyronine/thyroxine effect on target tissues (1%)

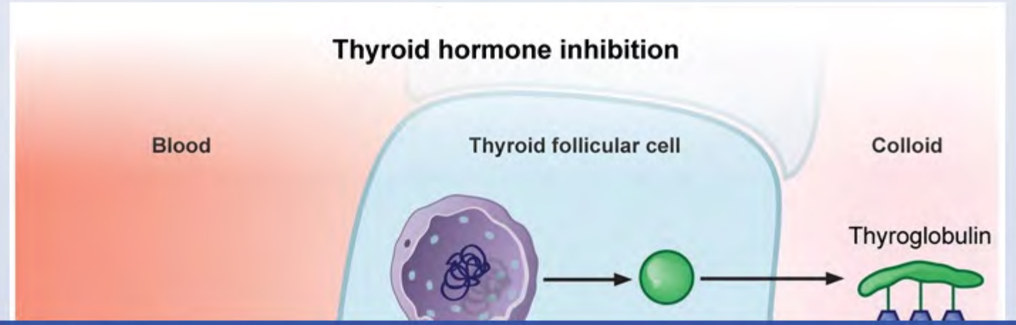
Incorrect
Correct answer
B

74%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation



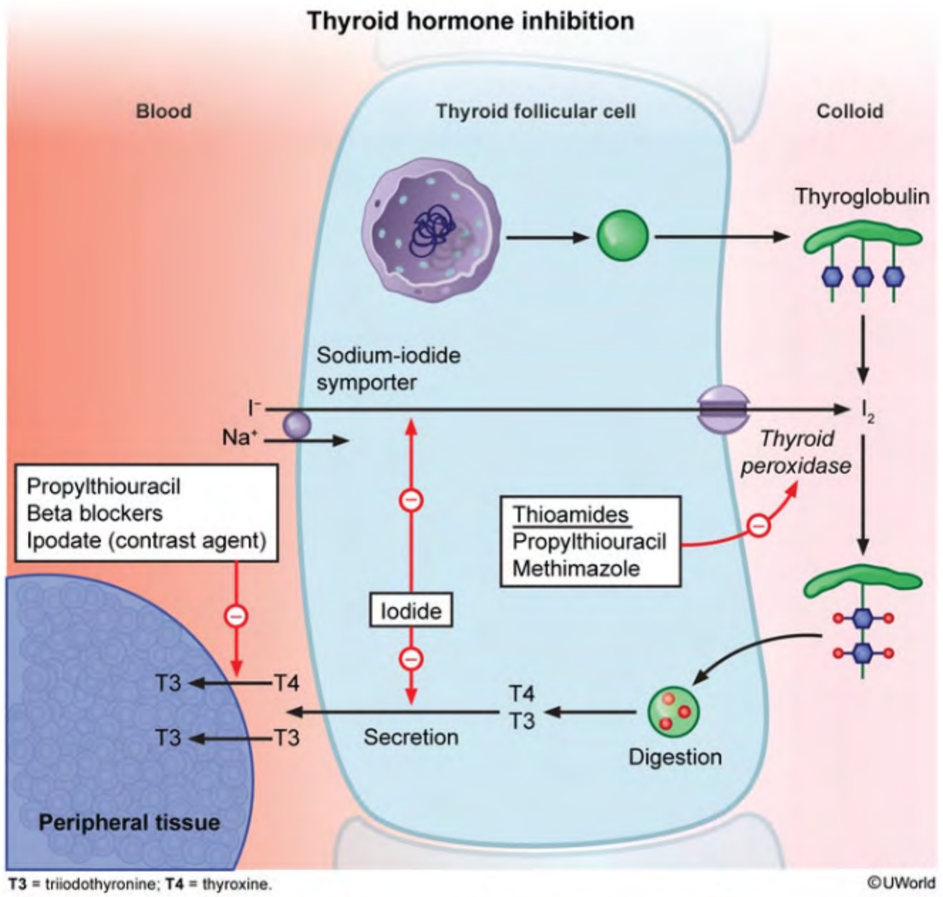
https://t.me/USMLEWorldStep1

A 22-year-old woman comes to the office due to palpitations, weight loss, and insomnia. She has lost 7 kg (15.4 lb) in t
tobacc
gland
and el
resolv
proces

Incc
Corre
B

Expl

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

T3 = triiodothyronine; **T4** = thyroxine.

©UWorld

Thyroid follicular cells take up inorganic iodide (iodide trapping) against a concentration gradient using a sodium-iodide symporter. Iodide is then released into the thyroid follicular lumen, where it is oxidized to iodine radical by thyroid peroxidase. Iodine then binds to tyrosine residues (organification) in thyroglobulin to form monoiodotyrosine (MIT) and diiodotyrosine (DIT). Coupling of MIT and DIT produces triiodothyronine (T3; MIT coupled with DIT) and thyroxine (T4; two DITs coupled). The thyroid follicular cells then engulf thyroglobulin, which contains the iodinated tyrosine compounds, via pinocytosis. In the thyroid cytoplasm, T3 and T4 (collectively, thyroid hormones) are removed from the rest of the thyroglobulin and secreted from the basolateral border.

This patient with elevated T4 and suppressed TSH has primary **hyperthyroidism**. Methimazole and propylthiouracil are **thioamide drugs** used for treating hyperthyroidism. They **inhibit thyroid peroxidase**, the enzyme responsible for both **iodine organification** and **coupling of iodotyrosines**. Propylthiouracil also decreases the peripheral conversion of T4 to the active hormone T3, although methimazole does not have this effect **(Choice D)**.

(Choice A) Colloid is a gelatinous material in the follicular lumen that consists mainly of thyroglobulin. The production of colloid is regulated primarily by TSH; it is not dependent on thyroid peroxidase and is not inhibited by thioamides.

(Choice C) Iodide uptake is upregulated by TSH. Perchlorate and pertechnetate are competitive inhibitors of the sodium-iodide symporter.

(Choice E) Hyperthyroidism is characterized by increased sensitivity to catecholamines due to the thyroid hormone–mediated upregulation of beta-adrenergic receptors. Beta blockers help decrease the target organ effects of thyroid hormones, and certain ones (eg, propranolol) also decrease the peripheral conversion of T4 to T3.

Educational objective:
Thioamides (eg, methimazole, propylthiouracil) decrease the formation of thyroid hormones via inhibition of thyroid peroxidase, the enzyme responsible for both iodine organification and coupling of iodotyrosines. Propylthiouracil also decreases the peripheral conversion of T4 to T3.

https://t.me/USMLEWorldStep1

T3 = triiodothyronine; T4 = thyroxine.

©UWorld

Thyroid follicular cells take up inorganic iodide (iodide trapping) against a concentration gradient using a sodium-
iodide
thyroid
monoi
couple
contai
thyroid

This p
propyl
enzym
decrea
effect

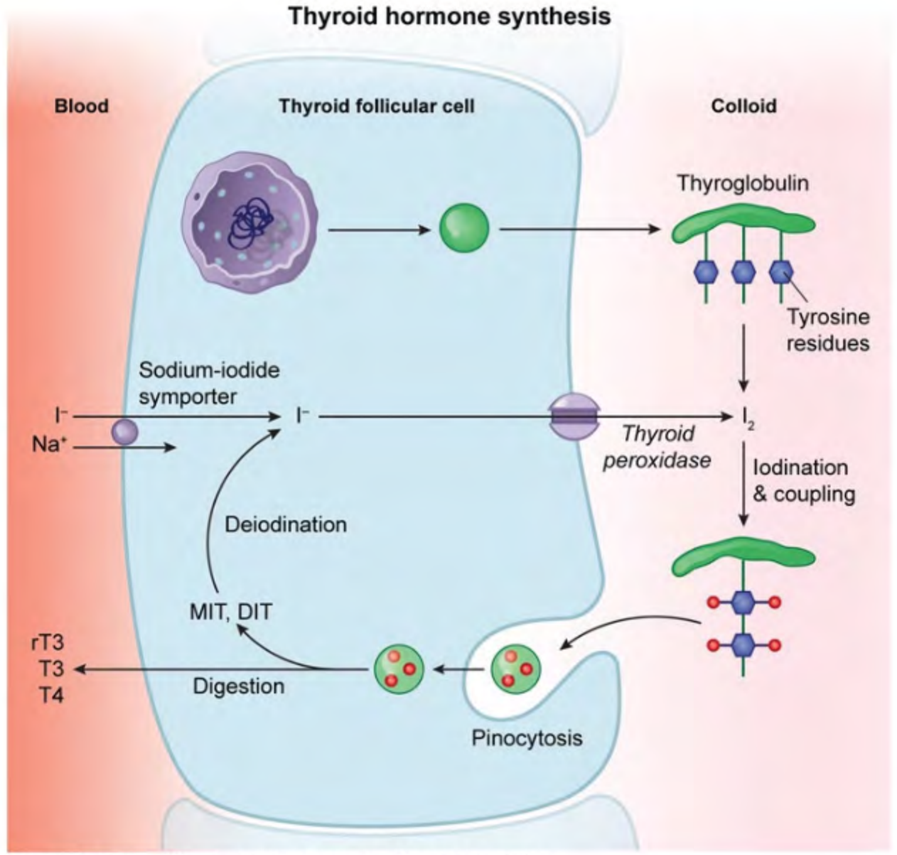
(Choi
produc
thioam

(Choi
sodiu

(Choi
hormo
effects
T3.

Educa
Thioar
peroxi
also decreases the peripheral conversion of T4 to T3.

Exhibit Display



DIT = diiodotyrosine; rT3 = reverse triiodothyronine; T3 = triiodothyronine; T4 = thyroxine; MIT = monoiodotyrosine.

©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

A 6-month-old boy is brought to the office for a well-child visit. He is babbling, sitting with support, and rolling over. The patient is exclusively breastfed and has not yet started solid foods. The parents note that he has been straining while passing stool, which has been hard in consistency, over the last few weeks. The patient was diagnosed with congenital hypothyroidism based on newborn screening results, and levothyroxine was initiated at age 2 weeks. He also takes daily vitamin D and iron supplements. The patient has no other chronic medical conditions. Vital signs are normal for age. Weight gain is appropriate for age, but length has decreased from the 60th to the 40th percentile since the last visit. Physical examination is unremarkable. Thyroid function testing at age 4 months was normal. Results of routine follow-up laboratory testing are as follows:

TSH	8.0 μU/mL
Free thyroxine	0.3 ng/dL (normal: 0.5-2.3)

Which of the following is the most likely mechanism for this patient's abnormal thyroid function tests?

- A. Decreased levothyroxine absorption
- B. Decreased thyroxine-binding globulin
- C. Excessive thyroid hormone supplementation
- D. Inadequate dietary iodine
- E. Thyroid hormone resistance

Submit

https://t.me/USMLEWorldStep1

A 6-month-old boy is brought to the office for a well-child visit. He is babbling, sitting with support, and rolling over. The patient is exclusively breastfed and has not yet started solid foods. The parents note that he has been straining while passing stool, which has been hard in consistency, over the last few weeks. The patient was diagnosed with congenital hypothyroidism based on newborn screening results, and levothyroxine was initiated at age 2 weeks. He also takes daily vitamin D and iron supplements. The patient has no other chronic medical conditions. Vital signs are normal for age. Weight gain is appropriate for age, but length has decreased from the 60th to the 40th percentile since the last visit. Physical examination is unremarkable. Thyroid function testing at age 4 months was normal. Results of routine follow-up laboratory testing are as follows:

TSH	8.0 µU/mL
Free thyroxine	0.3 ng/dL (normal: 0.5-2.3)

Which of the following is the most likely mechanism for this patient's abnormal thyroid function tests?

- ✓ A. Decreased levothyroxine absorption (47%)
- B. Decreased thyroxine-binding globulin (9%)
- C. Excessive thyroid hormone supplementation (5%)
- D. Inadequate dietary iodine (20%)
- E. Thyroid hormone resistance (16%)

Correct

47% Answered correctly

05 secs Time Spent

2023 Version

Explanation

Congenital hypothyroidism

https://t.me/USMLEWorldStep1

Congenital hypothyroidism	
Clinical manifestations	• Asymptomatic at birth • After maternal thyroxine wanes (weeks to months): ◦ Lethargy, poor feeding ◦ Enlarged fontanelle ◦ Protruding tongue, puffy face, umbilical hernia ◦ Constipation ◦ Prolonged jaundice ◦ Dry skin
Diagnosis	• ↑ TSH & ↓ free thyroxine levels • Newborn screening
Treatment	• Levothyroxine*
*Delayed treatment is associated with neurocognitive dysfunction (eg, ↓ intelligence quotient).	

This patient with **treated congenital hypothyroidism** has **elevated TSH** and **low free thyroxine (T4)**, findings concerning for **ineffective therapy** with synthetic thyroid hormone (ie, levothyroxine). The most common cause of inadequate thyroid hormone levels in infants with treated congenital hypothyroidism is **rapid growth**, which increases the physiologic need for thyroid hormone. Another common reason for ineffective therapy is **decreased absorption of levothyroxine**.

Coadministration with various foods (eg, soy products) or drugs (eg, **iron**, **calcium, antacids**) can lead to poor intestinal absorption of levothyroxine. In this case, iron binding to levothyroxine in the gastrointestinal tract caused circulating levothyroxine levels to decrease, resulting in symptoms of hypothyroidism (eg, constipation, poor linear growth) and increased TSH production. Because this patient's thyroid function tests at age 4 months were normal, iron supplementation was likely started in the past 2 months to treat the physiologic waning of iron stores that occurs at this age.

(Choice B) Thyroxine-binding globulin (TBG) deficiency is characterized by low total T4 but normal TSH and free

https://t.me/USMLEWorldStep1

Treatment	• Levothyroxine*

*Delayed treatment is associated with neurocognitive dysfunction (eg, ↓ intelligence quotient).

This patient with **treated congenital hypothyroidism** has **elevated TSH** and **low free thyroxine (T4)**, findings concerning for **ineffective therapy** with synthetic thyroid hormone (ie, levothyroxine). The most common cause of inadequate thyroid hormone levels in infants with treated congenital hypothyroidism is **rapid growth**, which increases the physiologic need for thyroid hormone. Another common reason for ineffective therapy is **decreased absorption of levothyroxine**.

Coadministration with various foods (eg, soy products) or drugs (eg, **iron**, **calcium, antacids**) can lead to poor intestinal absorption of levothyroxine. In this case, iron binding to levothyroxine in the gastrointestinal tract caused circulating levothyroxine levels to decrease, resulting in symptoms of hypothyroidism (eg, constipation, poor linear growth) and increased TSH production. Because this patient's thyroid function tests at age 4 months were normal, iron supplementation was likely started in the past 2 months to treat the physiologic waning of iron stores that occurs at this age.

(Choice B) Thyroxine-binding globulin (TBG) deficiency is characterized by low total T4 but normal TSH and free T4 levels. Patients do not require treatment because they are asymptomatic and euthyroid.

(Choice C) Excessive thyroid hormone supplementation would result in inhibition of TSH production and elevated T4 levels with signs of hyperthyroidism (eg, tachycardia, irritability, increased bowel movements).

(Choice D) Deficiency of iodine, which is required for thyroid hormone synthesis, rarely causes hypothyroidism in resource-rich countries due to dietary iodine found in salt. Breast milk also provides adequate iodine for infants, making this diagnosis unlikely.

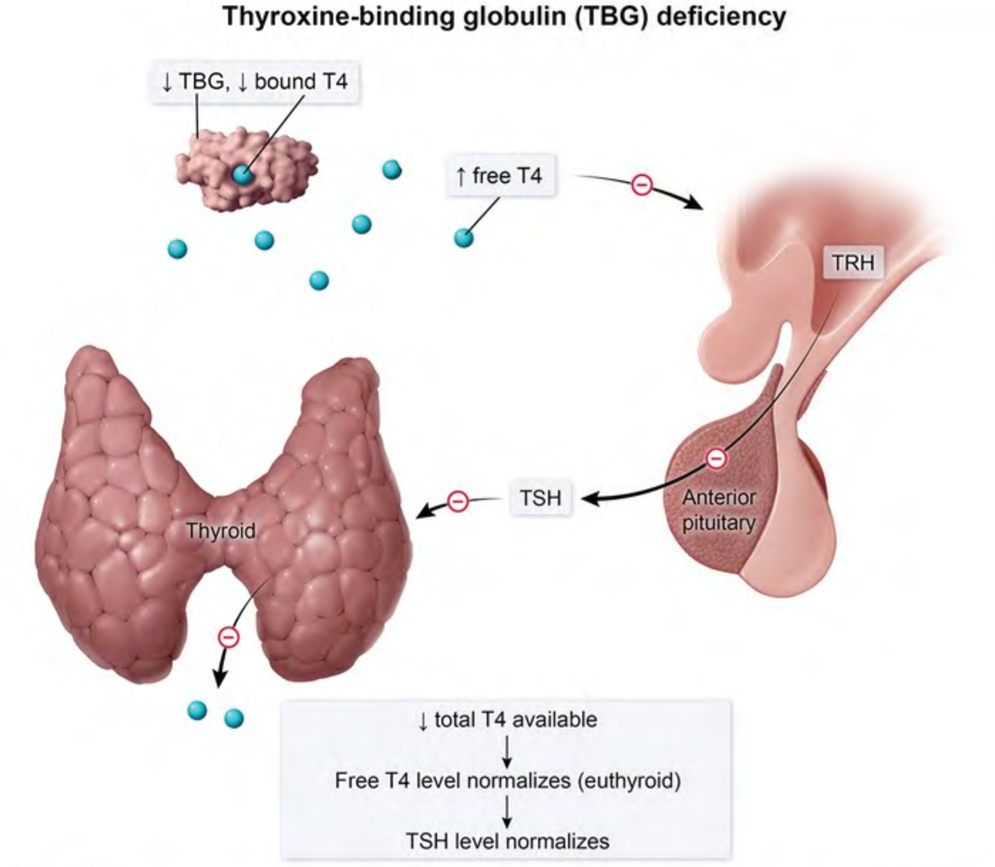
(Choice E) Thyroid hormone resistance is caused by thyroid hormone receptor mutations and results in elevated TSH and T4 levels due to impaired feedback inhibition. Signs of hypothyroidism or hyperthyroidism can occur due to varying tissue sensitivity to thyroid hormones.

Educational objective:
Coadministration of levothyroxine with various foods (eg, soy products) and certain medications (eg, iron, calcium, antacids) can lead to poor intestinal absorption of levothyroxine and symptoms of hypothyroidism while on therapy.

https://t.me/USMLEWorldStep1

Treatment	• Levothyroxine*

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

This p
concer
inadec
increa
absor

Coadr
intesti
cause
poor li
were r
stores

(Choi
T4 lev

(Choi
T4 lev

(Choi
resour
makin

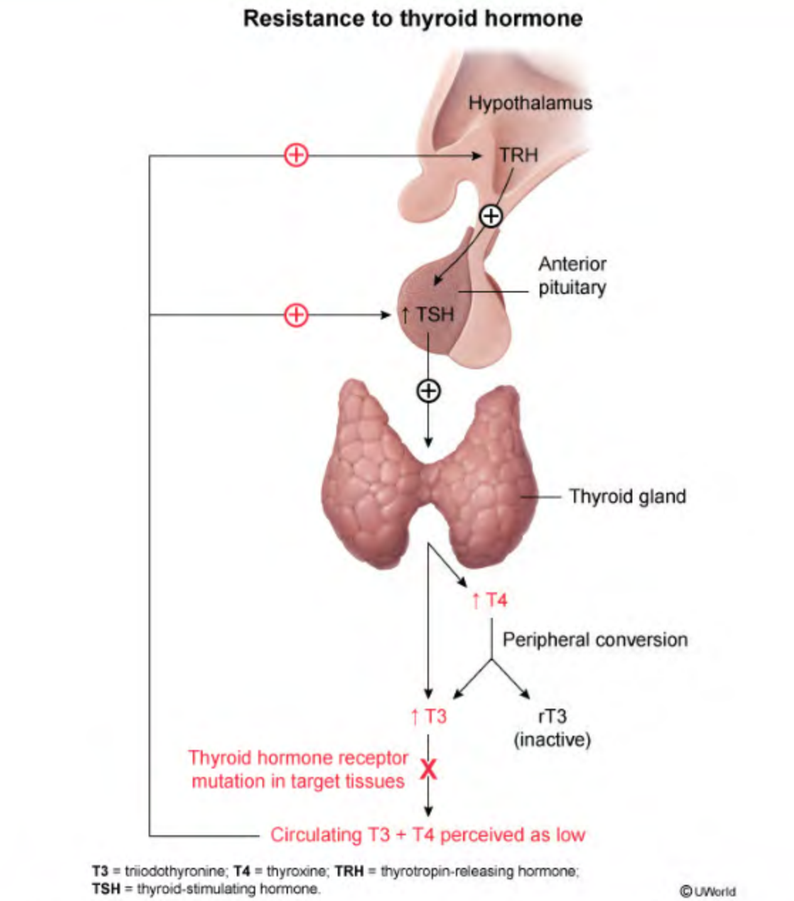
(Choi
TSH a
to vary

Educa
Coadministration of levothyroxine with various foods (eg, soy products) and certain medications (eg, iron, calcium, antacids) can lead to poor intestinal absorption of levothyroxine and symptoms of hypothyroidism while on therapy.

https://t.me/USMLEWorldStep1

Treatment	• Levothyroxine*

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

This p
concer
inadec
increa
absor

Coadr
intesti
cause
poor li
were r
stores

(Choi
T4 lev

(Choi
T4 lev

(Choi
resour
makin

(Choi
TSH a
to vary

Educa
Coadministration of levothyroxine with various foods (eg, soy products) and certain medications (eg, iron, calcium, antacids) can lead to poor intestinal absorption of levothyroxine and symptoms of hypothyroidism while on therapy.

https://t.me/USMLEWorldStep1

An infant is born at 39 weeks gestation to a 26-year-old woman. The delivery was uncomplicated, and Apgar scores were 8 and 9 at 1 and 5 minutes, respectively. The mother had gestational diabetes during pregnancy, which was controlled by diet alone. Physical examination of the infant shows clitoromegaly and partial fusion of the labioscrotal folds. Cytogenetic analysis reveals a 46,XX karyotype. Abdominal imaging shows bilateral adrenal hyperplasia. This patient is most likely deficient for an enzyme normally responsible for which of the following reactions?

- A. Cholesterol → Pregnenolone
- B. Dehydroepiandrosterone → Androstenedione
- C. Progesterone → 11-deoxycorticosterone
- D. Progesterone → 17-hydroxyprogesterone
- E. Testosterone → Dihydrotestosterone

Submit

https://t.me/USMLEWorldStep1

An infant is born at 39 weeks gestation to a 26-year-old woman. The delivery was uncomplicated, and Apgar scores were 8 and 9 at 1 and 5 minutes, respectively. The mother had gestational diabetes during pregnancy, which was controlled by diet alone. Physical examination of the infant shows clitoromegaly and partial fusion of the labioscrotal folds. Cytogenetic analysis reveals a 46,XX karyotype. Abdominal imaging shows bilateral adrenal hyperplasia. This patient is most likely deficient for an enzyme normally responsible for which of the following reactions?

- A. Cholesterol → Pregnenolone (2%)
- ✗ B. Dehydroepiandrosterone → Androstenedione (7%)
- ✓ C. Progesterone → 11-deoxycorticosterone (62%)
- D. Progesterone → 17-hydroxyprogesterone (24%)
- E. Testosterone → Dihydrotestosterone (3%)

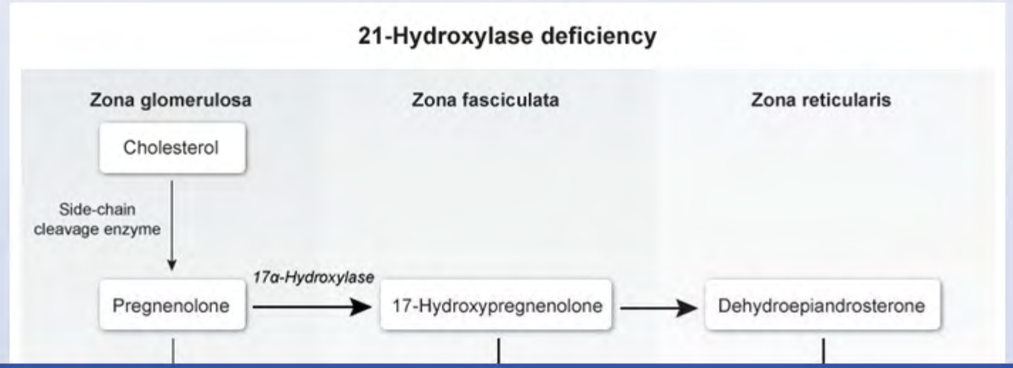
Incorrect
Correct answer
C

62%
Answered correctly

03 secs
Time Spent

2023
Version

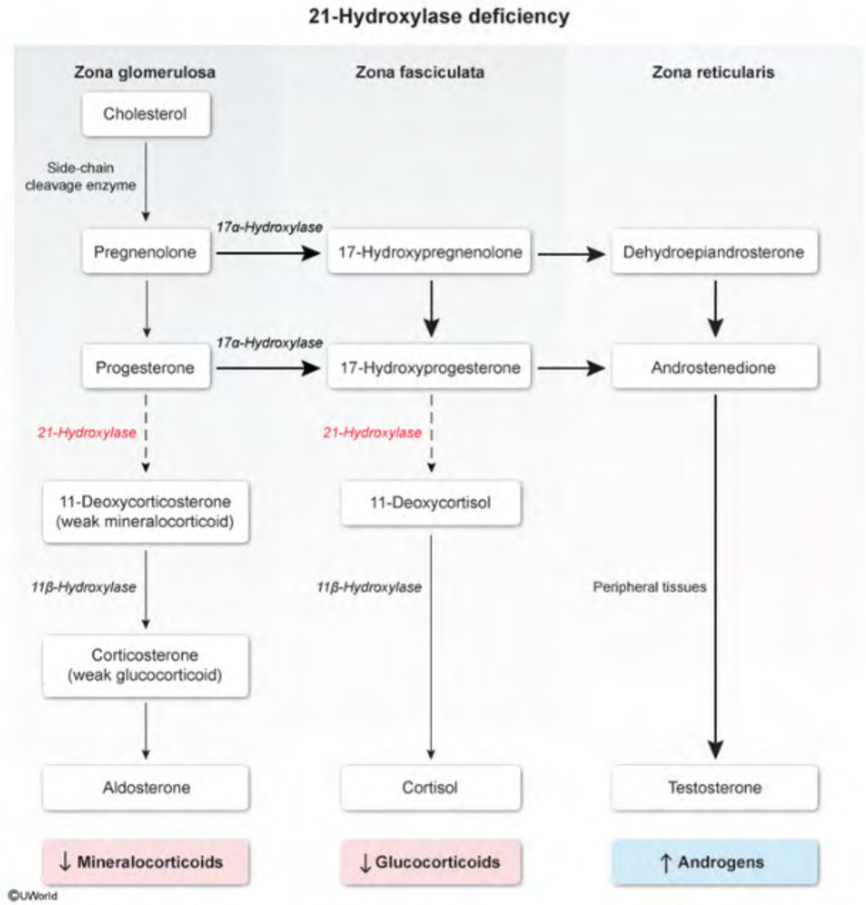
Explanation



https://t.me/USMLEWorldStep1

An infant is born at 39 weeks gestation to a 26-year-old woman. The delivery was uncomplicated, and Apgar scores
which
labios
hyperp
reactio

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

This patient's abdominal imaging and ambiguous genitalia are consistent with **congenital adrenal hyperplasia** (CAH). The most common cause of CAH is **21-hydroxylase deficiency**, accounting for 90% of all cases. This enzyme catalyzes the conversion of **progesterone to 11-deoxycorticosterone** (aldosterone precursor) in the zona glomerulosa, and 17-hydroxyprogesterone to 11-deoxycortisol (cortisol precursor) in the zona fasciculata.

In 21-hydroxylase deficiency, the adrenal gland cannot synthesize aldosterone and cortisol efficiently. ACTH levels increase as a result of low cortisol levels, stimulating **increased adrenal androgen** production by diverting the accumulating aldosterone and cortisol precursors toward the androgen biosynthetic pathway. Genetic females (46,XX) affected with classic 21-hydroxylase deficiency are usually identified at birth as increased androgen levels lead to ambiguous genitalia (**virilization**). However, genetic males (46,XY) have normal genitalia and therefore typically present later with symptoms of **salt-wasting** or precocious puberty.

Infants with 21-hydroxylase deficiency are often detected during routine newborn screening, and a high serum level of **17-hydroxyprogesterone** confirms the diagnosis.

(Choice A) Side-chain cleavage enzyme catalyzes the conversion of cholesterol into pregnenolone. Lack of this enzyme leads to absent steroid hormone synthesis. Complete enzyme deficiency is lethal due to absent placental progesterone synthesis.

(Choice B) Dehydroepiandrosterone is converted to androstenedione by 3β-hydroxysteroid dehydrogenase, an enzyme that also converts pregnenolone to progesterone and 17-hydroxypregnenolone to 17-hydroxyprogesterone. Although deficiency of this enzyme can result in adrenal insufficiency and ambiguous genitalia (in both sexes), it is a very rare cause of CAH.

(Choice D) Synthesis of 17-hydroxyprogesterone from progesterone is catalyzed by 17α-hydroxylase. Deficiency of this enzyme causes mineralocorticoid excess and impaired androgen synthesis. Genetic males have ambiguous genitalia, whereas genetic females appear phenotypically normal.

(Choice E) 5α-reductase deficiency prevents the conversion of testosterone to dihydrotestosterone, the hormone responsible for the development of male external genitalia. Affected genetic males, not females, are born with ambiguous genitalia.

Educational objective:

https://t.me/USMLEWorldStep1

zona glomerulosa, and 17-hydroxyprogesterone to 11-deoxycortisol (cortisol precursor) in the zona fasciculata.

In 21-hydroxylase deficiency, the adrenal gland cannot synthesize aldosterone and cortisol efficiently. ACTH levels increase as a result of low cortisol levels, stimulating **increased adrenal androgen** production by diverting the accumulating aldosterone and cortisol precursors toward the androgen biosynthetic pathway. Genetic females (46,XX) affected with classic 21-hydroxylase deficiency are usually identified at birth as increased androgen levels lead to ambiguous genitalia (**virilization**). However, genetic males (46,XY) have normal genitalia and therefore typically present later with symptoms of **salt-wasting** or precocious puberty.

Infants with 21-hydroxylase deficiency are often detected during routine newborn screening, and a high serum level of **17-hydroxyprogesterone** confirms the diagnosis.

(Choice A) Side-chain cleavage enzyme catalyzes the conversion of cholesterol into pregnenolone. Lack of this enzyme leads to absent steroid hormone synthesis. Complete enzyme deficiency is lethal due to absent placental progesterone synthesis.

(Choice B) Dehydroepiandrosterone is converted to androstenedione by 3β-hydroxysteroid dehydrogenase, an enzyme that also converts pregnenolone to progesterone and 17-hydroxypregnenolone to 17-hydroxyprogesterone. Although deficiency of this enzyme can result in adrenal insufficiency and ambiguous genitalia (in both sexes), it is a very rare cause of CAH.

(Choice D) Synthesis of 17-hydroxyprogesterone from progesterone is catalyzed by 17α-hydroxylase. Deficiency of this enzyme causes mineralocorticoid excess and impaired androgen synthesis. Genetic males have ambiguous genitalia, whereas genetic females appear phenotypically normal.

(Choice E) 5α-reductase deficiency prevents the conversion of testosterone to dihydrotestosterone, the hormone responsible for the development of male external genitalia. Affected genetic males, not females, are born with ambiguous genitalia.

Educational objective:
The most common form of congenital adrenal hyperplasia is 21-hydroxylase deficiency. Genetically female infants typically have ambiguous genitalia (virilization) at birth, whereas males have phenotypically normal genitalia, with salt-wasting or precocious puberty appearing later. Elevated 17-hydroxyprogesterone is diagnostic.

https://t.me/USMLEWorldStep1

zona glomerulosa, and 17-hydroxyprogesterone to 11-deoxycortisol (cortisol precursor) in the zona fasciculata.

In 21-H
increa
accum
(46,XX
lead to
typical

Infants
level c

(Choi
enzym
proges

(Choi
enzym
hydrox
genita

(Choi
of this
ambig

(Choi
respon
ambig

Educa
The m
typical
salt-wasting or precocious puberty appearing later. Elevated 17-hydroxyprogesterone is diagnostic.

Exhibit Display

21-Hydroxylase deficiency clinical syndromes

	Classic, salt wasting	Classic, non–salt wasting*	Nonclassic, late onset
Enzyme deficiency	Severe	Moderate	Mild
Clinical features	• Birth (girls): ambiguous genitalia • Age 1-2 weeks: vomiting, hypotension, hyperkalemia	• Birth (girls): ambiguous genitalia • Age 2-4: virilization (eg, body odor, pubic/axillary hair) & rapid growth	• School-aged: premature pubarche & rapid growth • Adolescence (girls): hirsutism, acne, oligomenorrhea
Laboratory features	• Increased 17-hydroxyprogesterone • Increased testosterone		

*Also called simple virilizing form.

New | Existing | My Notebook

https://t.me/USMLEWorldStep1

A 45-year-old man comes to the office due to a 6-month history of headache, sweating, and pain in his lower back, knees, and small joints of his hands. The pain increases with physical activity. He is unable to remove his wedding ring due to swollen fingers. The patient has also experienced excessive urination and loss of libido. Examination shows a prominent jaw and enlarged supraorbital ridges. The patient's hands are notably broad with thickened fingers. Multiple skin tags are noted on the nape of the neck. Laboratory evaluation reveals low serum testosterone levels. Which of the following is the most likely underlying cause of this patient's joint symptoms?

- A. Accumulation of iron
- B. Deposition of crystals
- C. Formation of noncaseating granulomas
- D. Hypertrophy of the articular cartilage
- E. Infiltration of macrophages

Submit

https://t.me/USMLEWorldStep1

A 45-year-old man comes to the office due to a 6-month history of headache, sweating, and pain in his lower back, knees, and small joints of his hands. The pain increases with physical activity. He is unable to remove his wedding ring due to swollen fingers. The patient has also experienced excessive urination and loss of libido. Examination shows a prominent jaw and enlarged supraorbital ridges. The patient's hands are notably broad with thickened fingers. Multiple skin tags are noted on the nape of the neck. Laboratory evaluation reveals low serum testosterone levels. Which of the following is the most likely underlying cause of this patient's joint symptoms?

- A. Accumulation of iron (10%)
- ✕ B. Deposition of crystals (5%)
- C. Formation of noncaseating granulomas (3%)
- ✓ D. Hypertrophy of the articular cartilage (75%)
- E. Infiltration of macrophages (4%)

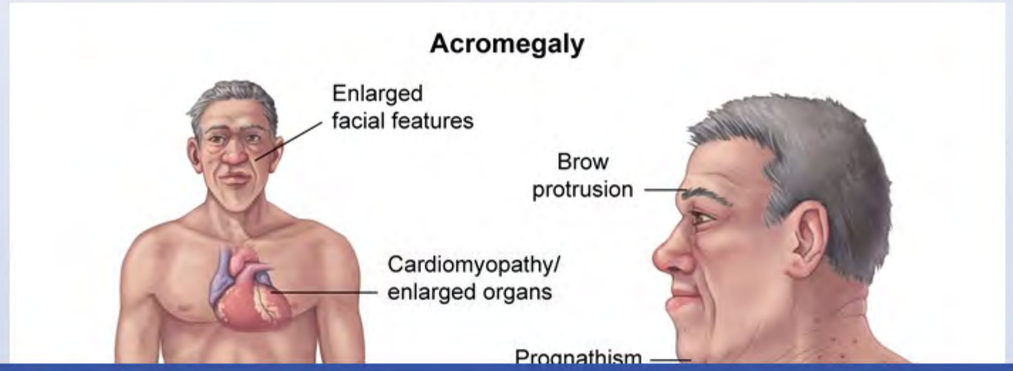
Incorrect
Correct answer
D

75%
Answered correctly

04 secs
Time Spent

2023
Version

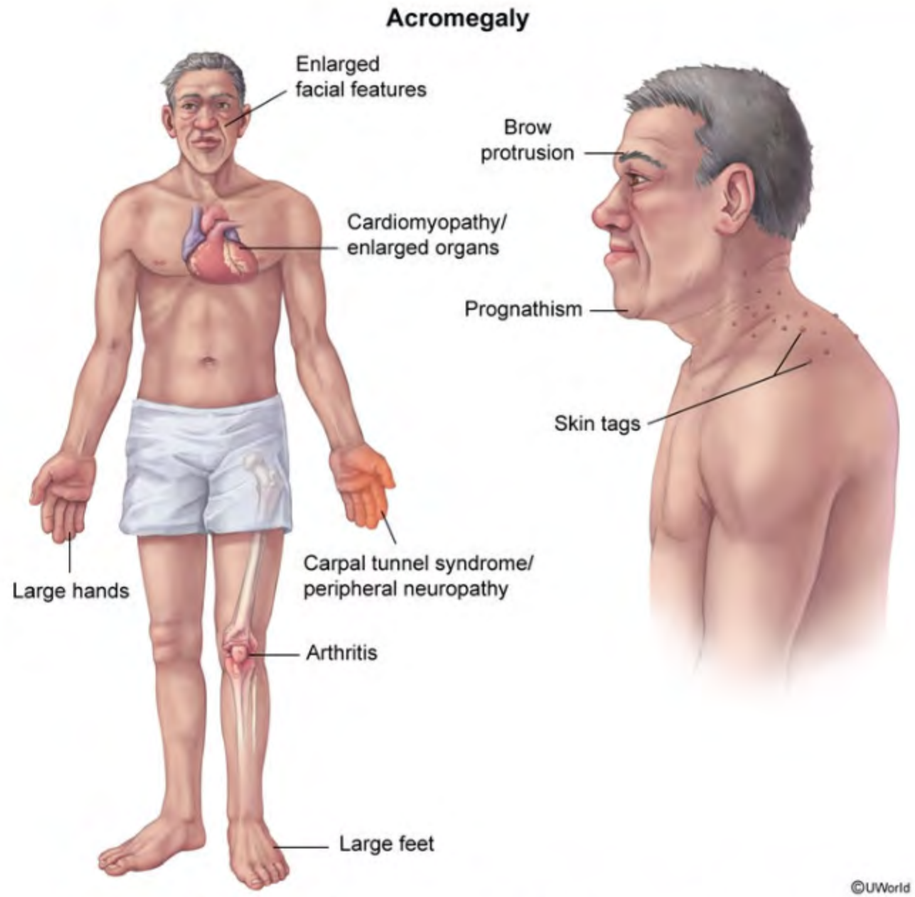
Explanation



https://t.me/USMLEWorldStep1

A 45-year-old man comes to the office due to a 6-month history of headache, sweating, and pain in his lower back, knees
weddi
Exami
thicke
testost

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Prognathism

https://t.me/USMLEWorldStep1

This patient has common features of **acromegaly**, including coarsening of facial features (eg, brow protrusion, prognathism), broadening of the hands, and skin involvement (eg, skin tags, hyperhidrosis). Acromegaly is caused by excessive production of **growth hormone** (GH) and is most often due to a **pituitary somatotroph adenoma**. Excess GH both directly and indirectly (via release of insulin-like growth factor-1 from the liver) leads to overgrowth of many tissues, including bone, cartilage, and visceral organs.

Acromegaly can affect the joints in both the axial and the appendicular skeleton. Excessive GH causes **hyperplasia of articular chondrocytes** and **synovial hypertrophy**, which may appear on x-ray as widening of the joint space. As acromegalic arthropathy continues, there is degeneration of articular cartilage and periarticular bone resembling osteoarthritis.

Complications of the pituitary mass itself include headache, visual field defects (compression of optic chiasm), and abnormalities of other pituitary hormones. **Hypogonadism** can occur secondary to hyperprolactinemia (from disrupted negative regulation of prolactin secretion) or directly due to compression of pituitary gonadotrophs.

(Choice A) Hereditary hemochromatosis (HH) can cause arthritis due to accumulation of iron in the articular cartilage and synovium. Although HH can also cause central hypogonadism, this patient's skeletal and facial features are more consistent with acromegaly.

(Choice B) Crystal deposition arthritis typically presents initially with acute inflammatory monarthritis at the first metatarsophalangeal joints and knees (gout), or knees, wrists, shoulders, and elbows (pseudogout [ie, calcium pyrophosphate deposition arthritis]). These disorders would not cause facial changes or hypogonadism.

(Choice C) Sarcoidosis is characterized by the formation of noncaseating granulomas in various tissues. Sarcoid arthropathy often occurs acutely in association with erythema nodosum and hilar adenopathy (Lofgren syndrome); chronic arthritis is less common and usually occurs in patients with significant pulmonary disease.

(Choice E) Rheumatoid arthritis (RA) involves a complex inflammatory response, culminating in an influx of monocytes that differentiate into inflammatory macrophages in the synovium. RA commonly presents with chronic swelling of the metacarpophalangeal joints but does not cause enlargement of the supraorbital ridges or jaw.

Educational objective:
Acromegaly can affect the joints in both the axial and the appendicular skeleton. Excessive growth hormone and

https://t.me/USMLEWorldStep1

Excess GH both directly and indirectly (via release of insulin-like growth factor-1 from the liver) leads to overgrowth of many tissues, including bone, cartilage, and visceral organs.

Acromegaly can affect the joints in both the axial and the appendicular skeleton. Excessive GH causes **hyperplasia of articular chondrocytes** and **synovial hypertrophy**, which may appear on x-ray as widening of the joint space. As acromegalic arthropathy continues, there is degeneration of articular cartilage and periarticular bone resembling osteoarthritis.

Complications of the pituitary mass itself include headache, visual field defects (compression of optic chiasm), and abnormalities of other pituitary hormones. **Hypogonadism** can occur secondary to hyperprolactinemia (from disrupted negative regulation of prolactin secretion) or directly due to compression of pituitary gonadotrophs.

(Choice A) Hereditary hemochromatosis (HH) can cause arthritis due to accumulation of iron in the articular cartilage and synovium. Although HH can also cause central hypogonadism, this patient's skeletal and facial features are more consistent with acromegaly.

(Choice B) Crystal deposition arthritis typically presents initially with acute inflammatory monarthritis at the first metatarsophalangeal joints and knees (gout), or knees, wrists, shoulders, and elbows (pseudogout [ie, calcium pyrophosphate deposition arthritis]). These disorders would not cause facial changes or hypogonadism.

(Choice C) Sarcoidosis is characterized by the formation of noncaseating granulomas in various tissues. Sarcoid arthropathy often occurs acutely in association with erythema nodosum and hilar adenopathy (Lofgren syndrome); chronic arthritis is less common and usually occurs in patients with significant pulmonary disease.

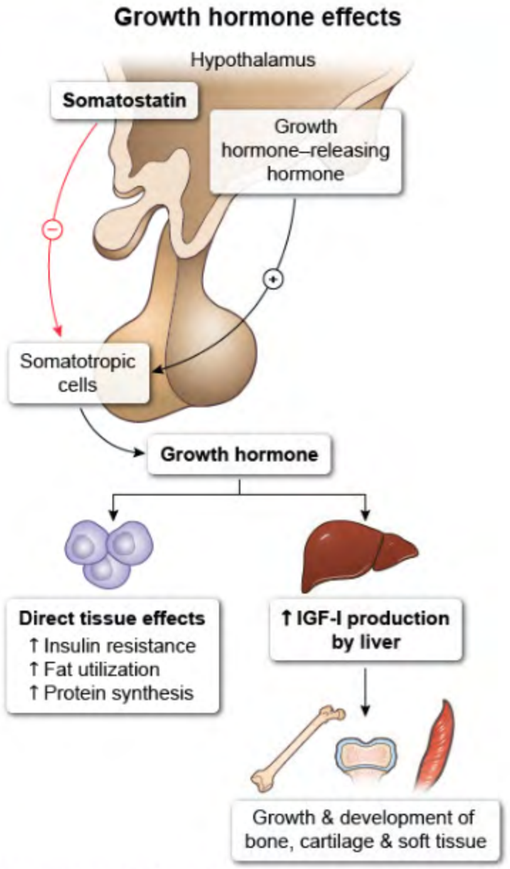
(Choice E) Rheumatoid arthritis (RA) involves a complex inflammatory response, culminating in an influx of monocytes that differentiate into inflammatory macrophages in the synovium. RA commonly presents with chronic swelling of the metacarpophalangeal joints but does not cause enlargement of the supraorbital ridges or jaw.

Educational objective:
Acromegaly can affect the joints in both the axial and the appendicular skeleton. Excessive growth hormone and insulin-like growth factor-1 cause hyperplasia of articular chondrocytes and synovial hypertrophy, leading to later degeneration of articular cartilage and periarticular bone.

https://t.me/USMLEWorldStep1



Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

This p
progna
by exc
Exces
of mar

Acrom
hyper
the joi
bone r

Compl
abnorr
disrup

(Choi
cartila
feature

(Choi
metata
pyroph

(Choice C) Sarcoidosis is characterized by the formation of noncaseating granulomas in various tissues. Sarcoid arthropathy often occurs acutely in association with erythema nodosum and hilar adenopathy (Lofgren syndrome);

https://t.me/USMLEWorldStep1

A 45-year-old previously healthy man comes to the office due to worsening muscle pain and weakness over the past 6 months. Carrying heavy items such as groceries has become increasingly difficult, and any prolonged activity causes diffuse muscle cramps. He has also had a 4.5-kg (10-lb) weight gain over this time. The patient takes no medications and does not use tobacco, alcohol, or illicit drugs. Blood pressure is 140/90 mm Hg and pulse is 56/min. BMI is 26 kg/m^2. Physical examination shows muscle weakness, predominantly of the shoulder and hip girdles. When the knee reflex is elicited, the quadriceps muscle contracts briskly but relaxation takes longer than normal. There are splitting and peeling of the nails. Serum creatine kinase is elevated. Which of the following tests is most likely to identify the cause of this patient's muscle weakness?

- A. 24-hour urinary cortisol excretion
- B. Acetylcholine receptor antibody titers
- C. CT scan of the chest
- D. Muscle biopsy
- E. Serum TSH level

Submit

https://t.me/USMLEWorldStep1

A 45-year-old previously healthy man comes to the office due to worsening muscle pain and weakness over the past 6 months. Carrying heavy items such as groceries has become increasingly difficult, and any prolonged activity causes diffuse muscle cramps. He has also had a 4.5-kg (10-lb) weight gain over this time. The patient takes no medications and does not use tobacco, alcohol, or illicit drugs. Blood pressure is 140/90 mm Hg and pulse is 56/min. BMI is 26 kg/m^2. Physical examination shows muscle weakness, predominantly of the shoulder and hip girdles. When the knee reflex is elicited, the quadriceps muscle contracts briskly but relaxation takes longer than normal. There are splitting and peeling of the nails. Serum creatine kinase is elevated. Which of the following tests is most likely to identify the cause of this patient's muscle weakness?

- A. 24-hour urinary cortisol excretion (12%)
- ✗ B. Acetylcholine receptor antibody titers (10%)
- C. CT scan of the chest (5%)
- D. Muscle biopsy (24%)
- ✓ E. Serum TSH level (46%)

Incorrect
Correct answer
E

46%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

Common causes of myopathy		
Disorder	**Clinical features**	**Creatine kinase**
Glucocorticoid-induced	• Progressive proximal muscle weakness & atrophy **without pain**	Normal

https://t.me/USMLEWorldStep1

Explanation

Common causes of myopathy		
Disorder	**Clinical features**	**Creatine kinase**
Glucocorticoid-induced myopathy	• Progressive proximal muscle weakness & atrophy **without pain** • Lower extremity muscles more involved	Normal
Polymyalgia rheumatica	• Muscle **pain & stiffness** in shoulder, neck & pelvic girdle • Worse in morning & with activity	Normal
Inflammatory myopathies (eg, polymyositis, dermatomyositis)	• Proximal muscle weakness • **Skin rash** & **inflammatory arthritis** possibly present	↑
Statin-induced myopathy	• Proximal muscle pain & weakness usually within weeks to months **after starting statin**	↑
Hypothyroid myopathy	• Muscle pain, cramps & weakness involving the proximal muscles • **Delayed tendon reflexes** & myoedema • Features of hypothyroidism	↑

An **elevated creatine kinase** (CK) level suggests a myopathic process with **myocyte damage** and release of muscle enzymes into the circulation. Common causes of myopathy with elevated CK include hypothyroidism, muscular dystrophies, inflammatory muscle diseases, and medications such as HMG-CoA reductase inhibitors.

https://t.me/USMLEWorldStep1

An **elevated creatine kinase** (CK) level suggests a myopathic process with **myocyte damage** and release of muscle enzymes into the circulation. Common causes of myopathy with elevated CK include hypothyroidism, muscular dystrophies, inflammatory muscle diseases, and medications such as HMG-CoA reductase inhibitors.

This patient's fatigue, **weight gain**, **bradycardia**, and **brittle nails** are highly suggestive of **hypothyroid myopathy**. Decreased thyroid hormone levels impair muscle glycogen and triglyceride use and increase oxidative stress, resulting in myocyte injury. Patients typically presents with myalgias, proximal muscle weakness, decreased exercise tolerance, and cramping. **Myoedema** (focal muscle contraction at the site of percussion) and **delayed relaxation** of deep tendon reflexes are characteristic findings that are caused by impaired reuptake of calcium by the sarcoplasmic reticulum.

Hypothyroid myopathy and elevations in CK can be the first signs of hypothyroidism and can precede other manifestations by months to years. The diagnosis can be confirmed with an **elevated TSH level**.

(Choice A) A 24-hour urine cortisol test is used as an initial test for Cushing syndrome. This disorder can present with proximal muscle weakness and atrophy due to the direct catabolic effects of cortisol on skeletal muscle. However, there is no associated muscle pain or rise in CK, reflexes are normal, and other cushingoid features (eg, stria, dorsocervical fatty hypertrophy) are usually present.

(Choices B and C) Myasthenia gravis is caused by autoantibodies against nicotinic acetylcholine receptors on the postsynaptic membrane of the neuromuscular junction. It presents with fluctuating weakness that worsens through the day. Lambert-Eaton syndrome is a paraneoplastic disorder associated with small cell carcinoma of the lung (which can be identified on CT scan). It is caused by autoantibodies against voltage-gated calcium channels on the presynaptic membrane, which cause decreased release of acetylcholine. These disorders affect the neuromuscular junction rather than the muscle itself, and CK is normal.

(Choice D) Muscle biopsy is often needed for diagnosis of inflammatory myositis (eg, polymyositis, dermatomyositis). However, this patient has symptoms suggestive of hypothyroidism (eg, weight gain, bradycardia, brittle nails), and histologic findings in hypothyroid myopathy are often nonspecific.

Educational objective:
Hypothyroid myopathy presents with myalgias, proximal muscle weakness, elevated creatine kinase levels, and

https://t.me/USMLEWorldStep1

This patient's fatigue, **weight gain**, **bradycardia**, and **brittle nails** are highly suggestive of **hypothyroid myopathy**. Decreased thyroid hormone levels impair muscle glycogen and triglyceride use and increase oxidative stress, resulting in myocyte injury. Patients typically presents with myalgias, proximal muscle weakness, decreased exercise tolerance, and cramping. **Myoedema** (focal muscle contraction at the site of percussion) and **delayed relaxation** of deep tendon reflexes are characteristic findings that are caused by impaired reuptake of calcium by the sarcoplasmic reticulum.

Hypothyroid myopathy and elevations in CK can be the first signs of hypothyroidism and can precede other manifestations by months to years. The diagnosis can be confirmed with an **elevated TSH level**.

(Choice A) A 24-hour urine cortisol test is used as an initial test for Cushing syndrome. This disorder can present with proximal muscle weakness and atrophy due to the direct catabolic effects of cortisol on skeletal muscle. However, there is no associated muscle pain or rise in CK, reflexes are normal, and other cushingoid features (eg, stria, dorsocervical fatty hypertrophy) are usually present.

(Choices B and C) Myasthenia gravis is caused by autoantibodies against nicotinic acetylcholine receptors on the postsynaptic membrane of the neuromuscular junction. It presents with fluctuating weakness that worsens through the day. Lambert-Eaton syndrome is a paraneoplastic disorder associated with small cell carcinoma of the lung (which can be identified on CT scan). It is caused by autoantibodies against voltage-gated calcium channels on the presynaptic membrane, which cause decreased release of acetylcholine. These disorders affect the neuromuscular junction rather than the muscle itself, and CK is normal.

(Choice D) Muscle biopsy is often needed for diagnosis of inflammatory myositis (eg, polymyositis, dermatomyositis). However, this patient has symptoms suggestive of hypothyroidism (eg, weight gain, bradycardia, brittle nails), and histologic findings in hypothyroid myopathy are often nonspecific.

Educational objective:
Hypothyroid myopathy presents with myalgias, proximal muscle weakness, elevated creatine kinase levels, and delayed relaxation of deep tendon reflexes. The diagnosis can be confirmed with an elevated TSH level. Other common causes of myopathy with elevated creatine kinase levels include inflammatory myopathies, muscular dystrophies, and HMG-CoA reductase inhibitors.

https://t.me/USMLEWorldStep1

A 28-year-old woman comes to the office due to progressively worsening eye irritation and double vision over the last 2 months. She also reports unintentional weight loss, mood swings, and palpitations. The patient has no prior medical problems and takes no medications. She has no known drug allergies and does not use tobacco, alcohol, or illicit drugs. Blood pressure is 140/70 mm Hg, and pulse is 110/min and regular. Physical examination shows bilateral conjunctival redness and severe proptosis. Appropriate therapy is begun. On a follow-up visit 4 weeks later, her eye symptoms have improved, and examination reveals a small decrease in proptosis with no redness. The drug that improved her ocular symptoms most likely did so by affecting which of the following?

- A. Inflammatory infiltration
- B. Iodine organification
- C. Iodine uptake by the thyroid
- D. Sympathetic hyperactivity
- E. T3/T4 release by the thyroid

Submit

https://t.me/USMLEWorldStep1

A 28-year-old woman comes to the office due to progressively worsening eye irritation and double vision over the last 2 months. She also reports unintentional weight loss, mood swings, and palpitations. The patient has no prior medical problems and takes no medications. She has no known drug allergies and does not use tobacco, alcohol, or illicit drugs. Blood pressure is 140/70 mm Hg, and pulse is 110/min and regular. Physical examination shows bilateral conjunctival redness and severe proptosis. Appropriate therapy is begun. On a follow-up visit 4 weeks later, her eye symptoms have improved, and examination reveals a small decrease in proptosis with no redness. The drug that improved her ocular symptoms most likely did so by affecting which of the following?

- ✓ A. Inflammatory infiltration (48%)
- B. Iodine organification (29%)
- C. Iodine uptake by the thyroid (3%)
- D. Sympathetic hyperactivity (8%)
- E. T3/T4 release by the thyroid (9%)

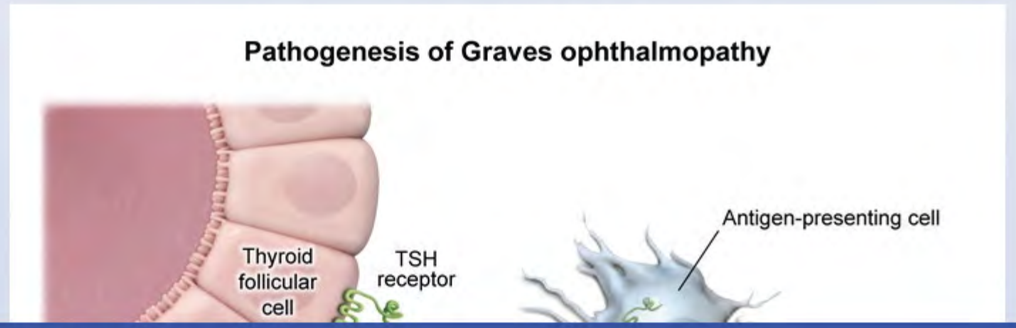
Correct

48% Answered correctly

05 secs Time Spent

2023 Version

Explanation



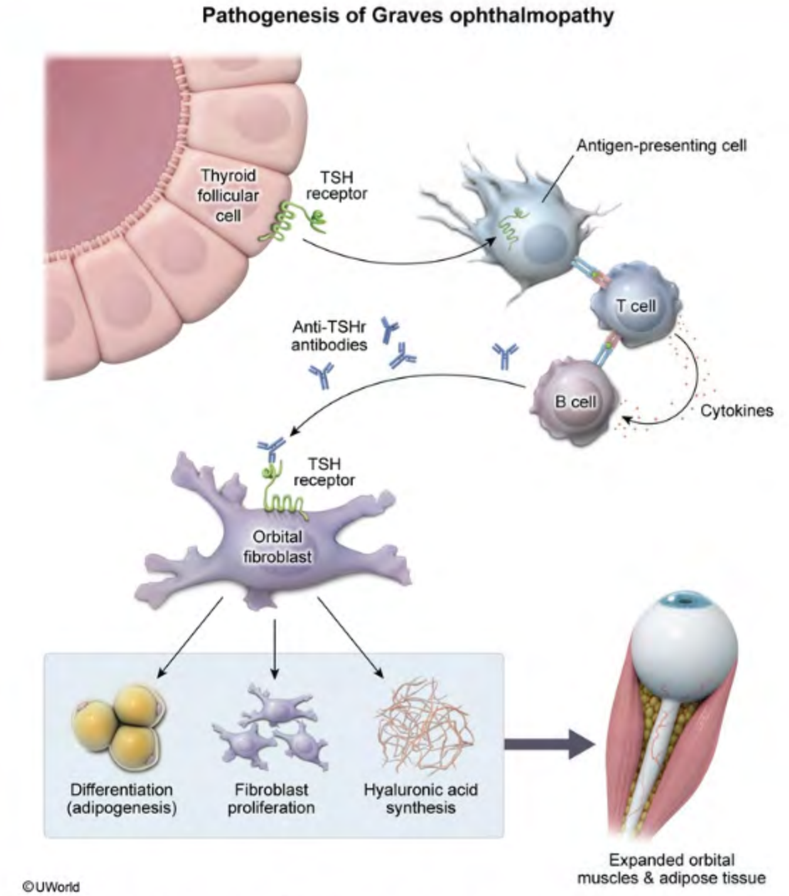
https://t.me/USMLEWorldStep1

A 28-year-old woman comes to the office due to progressively worsening eye irritation and double vision over the last 2
medic
or illici
bilater
later, h
The dr

Cor

Expl

Exhibit Display



Zoom In Zoom Out Reset New | Existing My Notebook

https://t.me/USMLEWorldStep1

This patient has **Graves disease** with hyperthyroidism (weight loss, palpitations, tachycardia) and significant ophthalmopathy (proptosis, diplopia). Graves disease is an autoimmune disorder triggered by **thyrotropin receptor antibodies**, which bind and activate the TSH receptor. In addition to the thyroid, the TSH receptor is present on fibroblasts, adipocytes, and other cell types. **Graves ophthalmopathy** is caused by stimulation of orbital fibroblasts by thyrotropin receptor antibodies, which leads to excess deposition of extracellular glycosaminoglycans; this is accompanied by T-cell activation and **inflammatory infiltration**. The resultant expansion of extraocular muscles and retro-orbital tissues with the orbit displaces the globe forward, and dysfunction of the extraocular muscles causes restricted extraocular movements and diplopia.

Glucocorticoids (eg, prednisone) decrease peripheral conversion of T4 to T3, but it is their **anti-inflammatory** effects that improve Graves ophthalmopathy. Glucocorticoids decrease the severity of inflammation and reduce the excess extraocular volume. They also can prevent worsening of ophthalmopathy induced by radioactive iodine treatment.

(Choices B, C, and E) Antithyroid drugs (eg, methimazole, propylthiouracil) inhibit thyroid peroxidase, leading to decreased iodine organification and coupling of iodotyrosines. Certain oxoanions (eg, perchlorate, pertechnetate) inhibit the sodium-iodide symporter and reduce iodine uptake by the thyroid. These agents ultimately lead to reduced production and release of thyroid hormone but do not alter the inflammatory process in Graves ophthalmopathy.

(Choice D) Sympathetic activation secondary to hyperthyroidism is responsible for a number of symptoms, including palpitations and tremors. Beta blockers can provide rapid symptomatic relief while awaiting definitive therapy. Although lid lag (which is seen in hyperthyroidism of any cause) would improve with beta blockers, the specific features of Graves ophthalmopathy (eg, diplopia, proptosis) would not be affected.

Educational objective:
Graves ophthalmopathy is caused by stimulation of orbital fibroblasts by thyrotropin receptor antibodies and cytokines released by activated T-cells. Excess deposition of extracellular glycosaminoglycans and inflammatory infiltration lead to expansion of extraocular muscles and retro-orbital tissues. Glucocorticoids improve Graves ophthalmopathy by decreasing the severity of inflammation and reducing the excess extraocular volume.

References

https://t.me/USMLEWorldStep1

This patient has **Graves disease** with hyperthyroidism (weight loss, palpitations, tachycardia) and significant
ophtha
recep
preser
orbital
glycos
expan
dysfur

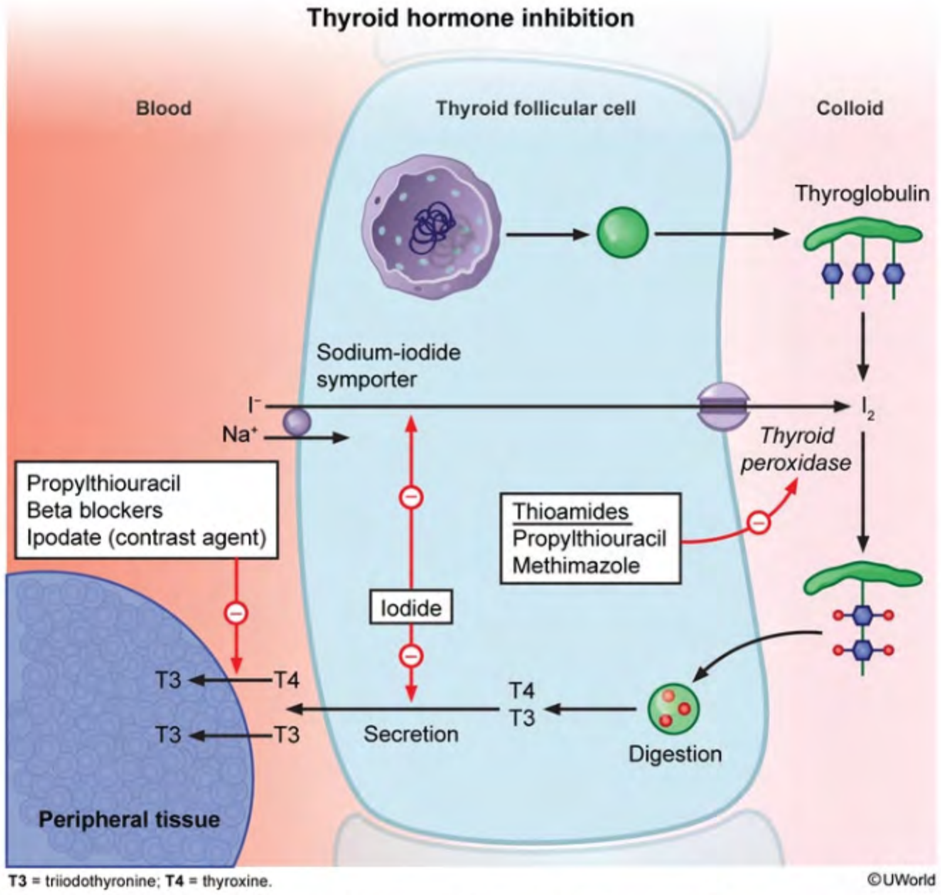
Gluco
effects
the ex
treatm

(Choi
decrea
inhibit
reduce
ophtha

(Choi
includi
therap
specifi

Educa
Grave
cytokir
infiltrat

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

ophthalmopathy by decreasing the severity of inflammation and reducing the excess extraocular volume.

References

A 34-year-old man comes to the clinic due to frequent clumsiness. For the last 6 months, he has had repeated minor injuries from walking into doorways and stationary objects. The patient was also reprimanded at work for causing his supervisor to spill coffee when he bumped into her in the hallway. Medical history is notable for recurrent renal stones; following a subsequent diagnostic evaluation, the patient underwent definitive treatment with neck surgery 3 years ago. Family history is unavailable as the patient was adopted. Physical examination reveals bitemporal visual field defects. Cranial nerves, motor strength, and deep-tendon reflexes are otherwise normal. In addition to brain imaging, this patient should also be screened for which of the following tumors?

- A. Adrenal
- B. Bone
- C. Breast
- D. Colonic
- E. Pancreatic

Submit

https://t.me/USMLEWorldStep1

A 34-year-old man comes to the clinic due to frequent clumsiness. For the last 6 months, he has had repeated minor injuries from walking into doorways and stationary objects. The patient was also reprimanded at work for causing his supervisor to spill coffee when he bumped into her in the hallway. Medical history is notable for recurrent renal stones; following a subsequent diagnostic evaluation, the patient underwent definitive treatment with neck surgery 3 years ago. Family history is unavailable as the patient was adopted. Physical examination reveals bitemporal visual field defects. Cranial nerves, motor strength, and deep-tendon reflexes are otherwise normal. In addition to brain imaging, this patient should also be screened for which of the following tumors?

- A. Adrenal
- B. Bone
- C. Breast
- D. Colonic
- E. Pancreatic

Submit

https://t.me/USMLEWorldStep1

A 34-year-old man comes to the clinic due to frequent clumsiness. For the last 6 months, he has had repeated minor injuries from walking into doorways and stationary objects. The patient was also reprimanded at work for causing his supervisor to spill coffee when he bumped into her in the hallway. Medical history is notable for recurrent renal stones; following a subsequent diagnostic evaluation, the patient underwent definitive treatment with neck surgery 3 years ago. Family history is unavailable as the patient was adopted. Physical examination reveals bitemporal visual field defects. Cranial nerves, motor strength, and deep-tendon reflexes are otherwise normal. In addition to brain imaging, this patient should also be screened for which of the following tumors?

- A. Adrenal (24%)
- ✗ B. Bone (9%)
- C. Breast (2%)
- D. Colonic (2%)
- ✓ E. Pancreatic (60%)

Incorrect
Correct answer
E

60%
Answered correctly

18 secs
Time Spent

2023
Version

Explanation

Classification of multiple endocrine neoplasia	
Type 1	• **Primary hyperparathyroidism** (parathyroid adenomas or hyperplasia) • Pituitary tumors (prolactin, visual defects) • Pancreatic tumors (especially gastrinomas)
	• **Medullary thyroid cancer** (calcitonin)

https://t.me/USMLEWorldStep1

Classification of multiple endocrine neoplasia	
Type 1	• **Primary hyperparathyroidism** (parathyroid adenomas or hyperplasia) • Pituitary tumors (prolactin, visual defects) • Pancreatic tumors (especially gastrinomas)
Type 2A	• **Medullary thyroid cancer** (calcitonin) • Pheochromocytoma • Primary hyperparathyroidism (parathyroid hyperplasia)
Type 2B	• **Medullary thyroid cancer** (calcitonin) • Pheochromocytoma • Mucosal neuromas/marfanoid habitus

Multiple endocrine neoplasia type 1 (MEN1) is caused by mutations in the *MEN1* tumor suppressor gene and is characterized by tumors of the **p**arathyroid gland, **p**ituitary, and **p**ancreas (the "**3 Ps**"). Primary hyperparathyroidism is often the initial manifestation and usually presents with asymptomatic hypercalcemia or **renal stones**. Prolactin-secreting adenomas (prolactinomas) are the most common pituitary tumors. In premenopausal women, prolactinomas typically present with metabolic symptoms (eg, menstrual irregularities, galactorrhea); in men and postmenopausal women they usually present later when tumor enlargement leads to mass effect symptoms such as headache or **bitemporal visual field defects** (causing clumsiness in this patient) due to compression of the optic chiasm.

Entero-pancreatic neuroendocrine tumors are the third major tumor type in MEN1. Gastrinoma (leading to Zollinger-Ellison syndrome) is the most common, followed by insulinoma and nonfunctional tumors. These tumors are often metastatic and are a frequent cause of tumor-related death in MEN1. This patient has visual field defects consistent with a pituitary mass lesion, which warrants cerebral imaging. In addition, he has a history of symptomatic hyperparathyroidism. Given these features of MEN1, he is also at increased risk for entero-

https://t.me/USMLEWorldStep1

- Mucosal neuromas/marfanoid habitus

Multiple endocrine neoplasia type 1 (MEN1) is caused by mutations in the *MEN1* tumor suppressor gene and is characterized by tumors of the **p**arathyroid gland, **p**ituitary, and **p**ancreas (the "**3 Ps**"). Primary hyperparathyroidism is often the initial manifestation and usually presents with asymptomatic hypercalcemia or **renal stones**. Prolactin-secreting adenomas (prolactinomas) are the most common pituitary tumors. In premenopausal women, prolactinomas typically present with metabolic symptoms (eg, menstrual irregularities, galactorrhea); in men and postmenopausal women they usually present later when tumor enlargement leads to mass effect symptoms such as headache or **bitemporal visual field defects** (causing clumsiness in this patient) due to compression of the optic chiasm.

Entero-pancreatic neuroendocrine tumors are the third major tumor type in MEN1. Gastrinoma (leading to Zollinger-Ellison syndrome) is the most common, followed by insulinoma and nonfunctional tumors. These tumors are often metastatic and are a frequent cause of tumor-related death in MEN1. This patient has visual field defects consistent with a pituitary mass lesion, which warrants cerebral imaging. In addition, he has a history of symptomatic hyperparathyroidism. Given these features of MEN1, he is also at increased risk for entero-pancreatic neuroendocrine tumors.

(Choice A) Pheochromocytoma is an adrenal medullary tumor that occurs commonly in MEN2A and 2B. However, this patient's visual field defect suggests a pituitary tumor, which is more characteristic of MEN1 (not associated with pheochromocytoma).

(Choice B) Primary bone tumors are not increased in MEN1, although malignant neuroendocrine tumors may occasionally metastasize to bone.

(Choice C) The major inherited syndromes associated with breast cancer include *BRCA1* and *BRCA2* mutations (breast, ovarian, uterine/fallopian tube, pancreatic cancers). Less common syndromes include Cowden syndrome, Li-Fraumeni syndrome, and Peutz-Jeghers syndrome. Hyperparathyroidism and pituitary tumors are not prominent manifestations of any of these syndromes and are more consistent with MEN1.

(Choice D) Familial adenomatous polyposis is associated with an increased risk of colon cancer and with adrenal adenomas and thyroid cancer.

Educational objective:

https://t.me/USMLEWorldStep1

hyperparathyroidism is often the initial manifestation and usually presents with asymptomatic hypercalcemia or **renal stones**. Prolactin-secreting adenomas (prolactinomas) are the most common pituitary tumors. In premenopausal women, prolactinomas typically present with metabolic symptoms (eg, menstrual irregularities, galactorrhea); in men and postmenopausal women they usually present later when tumor enlargement leads to mass effect symptoms such as headache or **bitemporal visual field defects** (causing clumsiness in this patient) due to compression of the optic chiasm.

Entero-pancreatic neuroendocrine tumors are the third major tumor type in MEN1. Gastrinoma (leading to Zollinger-Ellison syndrome) is the most common, followed by insulinoma and nonfunctional tumors. These tumors are often metastatic and are a frequent cause of tumor-related death in MEN1. This patient has visual field defects consistent with a pituitary mass lesion, which warrants cerebral imaging. In addition, he has a history of symptomatic hyperparathyroidism. Given these features of MEN1, he is also at increased risk for entero-pancreatic neuroendocrine tumors.

(Choice A) Pheochromocytoma is an adrenal medullary tumor that occurs commonly in MEN2A and 2B. However, this patient's visual field defect suggests a pituitary tumor, which is more characteristic of MEN1 (not associated with pheochromocytoma).

(Choice B) Primary bone tumors are not increased in MEN1, although malignant neuroendocrine tumors may occasionally metastasize to bone.

(Choice C) The major inherited syndromes associated with breast cancer include *BRCA1* and *BRCA2* mutations (breast, ovarian, uterine/fallopian tube, pancreatic cancers). Less common syndromes include Cowden syndrome, Li-Fraumeni syndrome, and Peutz-Jeghers syndrome. Hyperparathyroidism and pituitary tumors are not prominent manifestations of any of these syndromes and are more consistent with MEN1.

(Choice D) Familial adenomatous polyposis is associated with an increased risk of colon cancer and with adrenal adenomas and thyroid cancer.

Educational objective:
Multiple endocrine neoplasia type 1 syndrome is characterized by tumors of the pituitary, parathyroid gland, and pancreas (the "3 Ps").

References

https://t.me/USMLEWorldStep1

A 45-year-old man comes to the office due to slowly progressive back and joint pain. In particular, his knee and ankle joints are stiff and painful when he walks. Over the past year, the patient has also experienced excessive sweating, and his ring and shoe sizes have increased. He has no prior medical issues and takes no medications. The patient does not use tobacco, alcohol, or illicit drugs. There is no significant family history. Physical examination shows coarse facial features with a prominent forehead, protruding jaw, and widely separated maxillary teeth. There is mild swelling and crepitus of the knees and ankles bilaterally. Which of the following is most likely to be associated with this patient's condition?

- A. Aortic root dilation
- B. Bicuspid aortic valve
- C. Left ventricular hypertrophy
- D. Mitral valve prolapse
- E. Pericardial effusion

Submit

https://t.me/USMLEWorldStep1

A 45-year-old man comes to the office due to slowly progressive back and joint pain. In particular, his knee and ankle joints are stiff and painful when he walks. Over the past year, the patient has also experienced excessive sweating, and his ring and shoe sizes have increased. He has no prior medical issues and takes no medications. The patient does not use tobacco, alcohol, or illicit drugs. There is no significant family history. Physical examination shows coarse facial features with a prominent forehead, protruding jaw, and widely separated maxillary teeth. There is mild swelling and crepitus of the knees and ankles bilaterally. Which of the following is most likely to be associated with this patient's condition?

- ✗ A. Aortic root dilation (18%)
- B. Bicuspid aortic valve (3%)
- ✓ C. Left ventricular hypertrophy (66%)
- D. Mitral valve prolapse (10%)
- E. Pericardial effusion (2%)

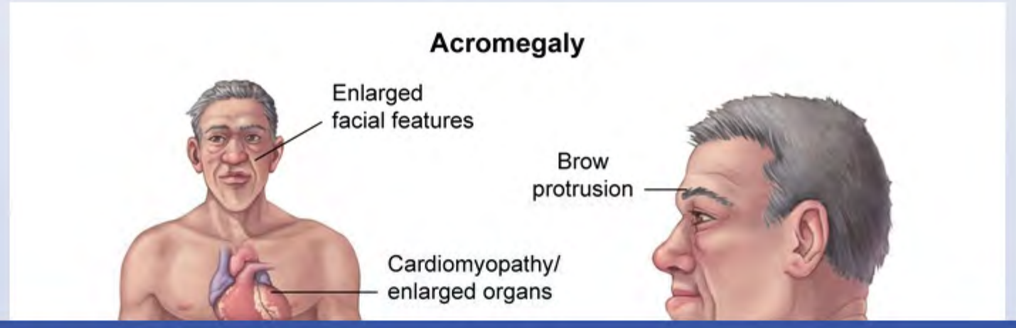
Incorrect
Correct answer
C

66%
Answered correctly

04 secs
Time Spent

2023
Version

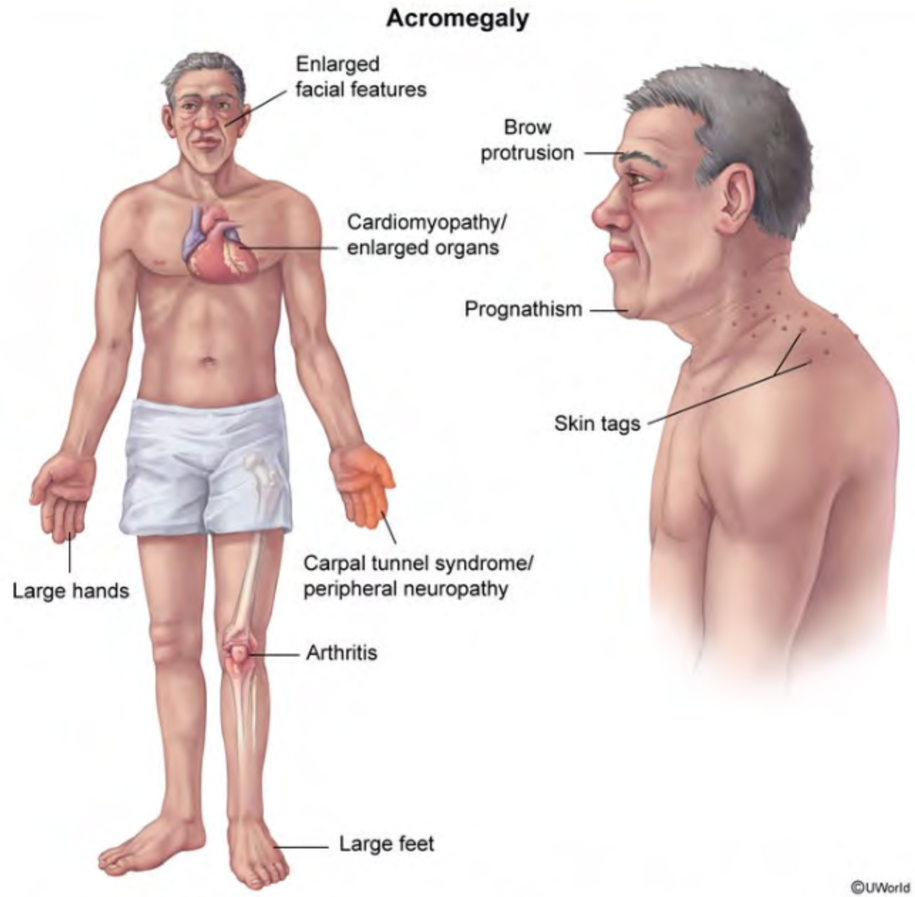
Explanation



https://t.me/USMLEWorldStep1

A 45-year-old man comes to the office due to slowly progressive back and joint pain. In particular, his knee and ankle j
sweati
The pa
exami
maxilla
most li

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Cardiomyopathy/ enlarged organs

https://t.me/USMLEWorldStep1

©UWorld

This patient has bony overgrowth (ie, frontal bossing; enlarged jaw, hands, and feet) consistent with acromegaly. **Acromegaly** is caused by excessive production of **growth hormone** (GH) and is most often due to a pituitary somatotroph adenoma. Excess GH both directly and indirectly (via release of insulin-like growth factor 1 from the liver) leads to overgrowth of many tissues, including bone, cartilage, and visceral organs.

In the heart, chronic GH elevation stimulates cardiac growth, causing **left ventricular hypertrophy**, diastolic dysfunction, and possible heart failure. The joints are also frequently involved in acromegaly, as excessive GH causes hyperplasia of articular chondrocytes and synovial hypertrophy, leading to wear and degeneration of articular cartilage and periarticular bone (hypertrophic **arthropathy**). Soft tissue involvement is also common and manifests as macroglossia, deepening of the voice (due to laryngeal soft tissue growth), carpal tunnel syndrome, and peripheral neuropathy.

(Choices A and D) Marfan syndrome is an inherited condition caused by a defect in fibrillin-1. Cardiovascular complications include cystic medial degeneration of the aorta (with aneurysmal dilation and dissection), aortic regurgitation, and mitral valve prolapse. However, unlike the bony enlargement in acromegaly, the typical marfanoid habitus is characterized by a tall, slender build and an increased ratio of limb length-to-height.

(Choice B) Ehlers-Danlos syndrome is due to an autosomal recessive defect in lysyl hydroxylase, which leads to defects in connective tissues (eg, fragile, hyperextensible skin). Musculoskeletal manifestations include hypermobile joints, pectus excavatum, and scoliosis. Valvular heart disease is common and can present as bicuspid aortic valve or mitral/tricuspid valve prolapse.

(Choice E) Patients with untreated hypothyroidism can have a pericardial effusion, and also frequently have nonpitting edema (myxedema) due to excessive deposition of mucopolysaccharides and adipogenesis in the dermis and subcutaneous tissues. However, bony enlargement is not characteristic.

Educational objective:
Acromegaly is caused by excessive production of growth hormone, usually due to a pituitary somatotroph adenoma. Musculoskeletal manifestations include bony hypertrophy (eg, frontal bossing; enlarged jaw, hands, and feet) and osteoarthritis. Left ventricular hypertrophy is often common in acromegaly and may progress to heart failure.

https://t.me/USMLEWorldStep1

This patient has bony overgrowth (ie, frontal bossing; enlarged jaw, hands, and feet) consistent with acromegaly.

Acron
somat
liver) l

In the
dysfun
cause
articul
manife
and pe

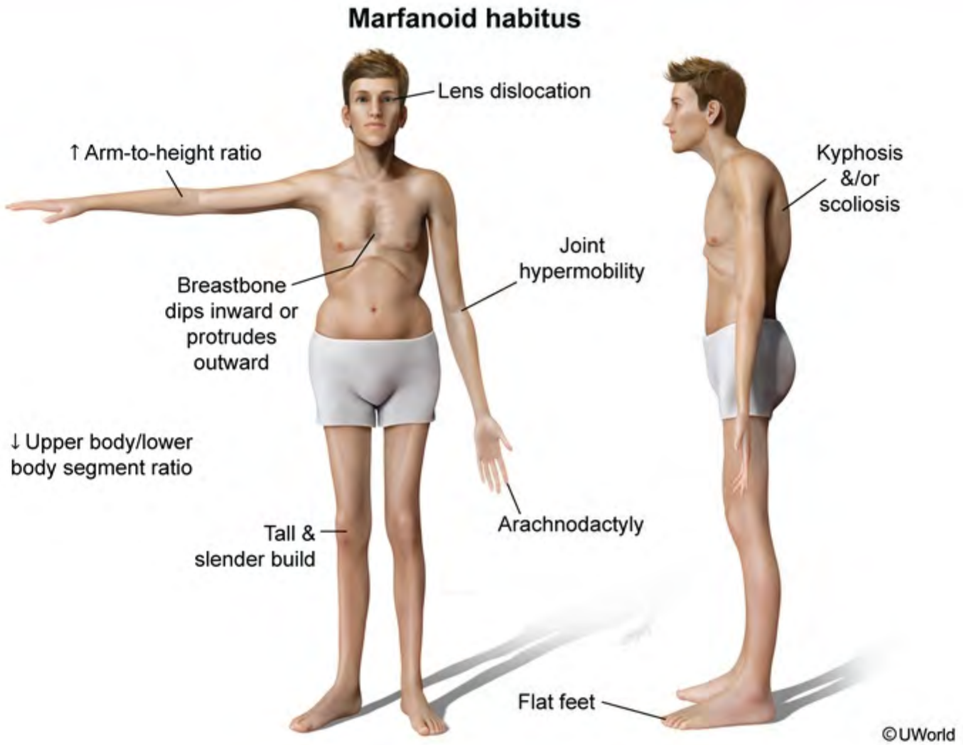
(Choi
compli
regurg
marfa

(Choi
defect
hyperr
bicusp

(Choi
nonpit
dermis

Educa
Acrom
adenoma. Musculoskeletal manifestations include bony hypertrophy (eg, frontal bossing; enlarged jaw, hands, and feet) and osteoarthritis. Left ventricular hypertrophy is often common in acromegaly and may progress to heart failure.

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

A 67-year-old woman comes to the office for follow-up of type 2 diabetes mellitus. She was diagnosed with diabetes 6 months ago. Lifestyle modification was initially advised, but the patient had no significant glycemic improvement. One month ago, the patient was started on metformin; however, she has been experiencing abdominal discomfort and diarrhea attributed to the therapy. She has no other medical conditions. BMI is 28 kg/m^2. Physical examination is unremarkable. Laboratory tests show hemoglobin A1c is 8.2%. After further discussion and with medication affordability taken into consideration, metformin is discontinued and glipizide is prescribed. Compared to metformin, this new therapy is most likely to increase the risk of which of the following?

- A. Acute pancreatitis
- B. Renal dysfunction
- C. Symptomatic hypoglycemia
- D. Vitamin B_{12} deficiency
- E. Vulvovaginal candidiasis

Submit

https://t.me/USMLEWorldStep1

A 67-year-old woman comes to the office for follow-up of type 2 diabetes mellitus. She was diagnosed with diabetes 6 months ago. Lifestyle modification was initially advised, but the patient had no significant glycemic improvement. One month ago, the patient was started on metformin; however, she has been experiencing abdominal discomfort and diarrhea attributed to the therapy. She has no other medical conditions. BMI is 28 kg/m^2. Physical examination is unremarkable. Laboratory tests show hemoglobin A1c is 8.2%. After further discussion and with medication affordability taken into consideration, metformin is discontinued and glipizide is prescribed. Compared to metformin, this new therapy is most likely to increase the risk of which of the following?

- ✗ A. Acute pancreatitis (8%)
- B. Renal dysfunction (6%)
- ✓ C. Symptomatic hypoglycemia (76%)
- D. Vitamin B_{12} deficiency (1%)
- E. Vulvovaginal candidiasis (6%)

Incorrect
Correct answer
C

76%
Answered correctly

04 secs
Time Spent

2023
Version

Explanation

Noninsulin antidiabetic agents for type 2 diabetes mellitus

Agent	Mechanism of action	Adverse effects
Insulin secretagogues • Sulfonylureas • Meglitinides	↑ Insulin secretion by inhibiting β-cell K_{ATP} channels	• Hypoglycemia • Weight gain
	Stimulate AMPK & inhibit mitochondrial	

https://t.me/USMLEWorldStep1

Noninsulin antidiabetic agents for type 2 diabetes mellitus		
Agent	**Mechanism of action**	**Adverse effects**
Insulin secretagogues • Sulfonylureas • Meglitinides	↑ Insulin secretion by inhibiting β-cell K_{ATP} channels	• Hypoglycemia • Weight gain
Biguanides • Metformin	Stimulate AMPK & inhibit mitochondrial gluconeogenesis, ↓ hepatic glucose production & ↑ peripheral glucose uptake	• Diarrhea • Lactic acidosis
Thiazolidinediones • Pioglitazone	Activate transcription regulator PPAR-γ, ↓ insulin resistance	• Fluid retention/heart failure • Weight gain
GLP-1 agonists • Exenatide • Liraglutide	↑ Glucose-dependent insulin secretion, ↓ glucagon secretion, delayed gastric emptying	• Pancreatitis • Weight loss
DPP4 inhibitors • Sitagliptin • Saxagliptin	↑ Endogenous GLP-1 & GIP levels	• Nasopharyngitis
SGLT-2 inhibitors • Canagliflozin • Dapagliflozin	↑ Renal glucose excretion	• Urinary tract infections • Hypotension
AMPK = AMP-activated protein kinase; **DPP4** = dipeptidyl peptidase-4; **GIP** = gastric inhibitory polypeptide; **GLP-1** = glucagon-like peptide-1; **K_{ATP}** = ATP-sensitive potassium; **PPAR-γ** = peroxisome proliferator–activated receptor γ; **SGLT-2** = sodium-glucose cotransporter-2.		

Metformin is the preferred initial medication for most patients with type 2 diabetes due to its low cost, lack of weight gain, and low risk of hypoglycemia. However, metformin can cause gastrointestinal side effects (eg, nausea

https://t.me/USMLEWorldStep1

Metformin is the preferred initial medication for most patients with type 2 diabetes due to its low cost, lack of weight gain, and low risk of hypoglycemia. However, metformin can cause gastrointestinal side effects (eg, nausea, diarrhea), which may be severe enough to warrant therapeutic change. Sulfonylureas are not typically preferred second-line agents; however, they are affordable and may be used as add-on therapy or as a replacement for metformin when cost is a major concern.

Sulfonylureas inhibit the ATP-sensitive potassium channel on the pancreatic beta cell membrane, inducing depolarization and L-type calcium channel opening. The increased Ca^{2+} influx stimulates beta cell **insulin release independent** of blood glucose concentrations (eg, even when blood glucose levels are normal or low). Therefore, a main associated risk is **hypoglycemia**. Circumstances that can lead to hypoglycemia include exercise, missed meals, or initiation of additional antidiabetic medications. Longer-acting sulfonylureas (eg, glyburide) are more prone to causing hypoglycemia than shorter-acting drugs (eg, glipizide) and are therefore not preferred.

(Choice A) Glucagon-like peptide-1 (GLP-1) helps regulate glucose by slowing gastric emptying and increasing insulin release in response to food intake. Pharmacologic GLP-1 agonists (eg, exenatide) lower blood glucose and promote weight loss; these agents are associated with acute pancreatitis.

(Choice B) In patients with poor oral intake (eg, gastroenteritis) or in those who are on concurrent diuretics (eg, furosemide), osmotic diuresis caused by sodium-glucose cotransporter 2 (SGLT2) inhibitors can lead to additional dehydration, resulting in acute kidney injury. In the long term, however, SGLT2 inhibitors have renoprotective effects and are recommended in patients with diabetic nephropathy.

(Choice D) Metformin can decrease absorption of vitamin B_{12}, leading to B_{12} deficiency in long-term use. Sulfonylureas do not have a significant effect on vitamin B_{12} metabolism.

(Choice E) SGLT2 inhibitors (eg, dapagliflozin) decrease renal reabsorption of glucose, leading to increased urinary glucose loss and lower blood glucose levels. The excess glucose in the urine can increase the risk of urinary tract infections and vulvovaginal candidiasis.

Educational objective:
Sulfonylureas inhibit the ATP-sensitive potassium channel on the pancreatic beta cell membrane, inducing depolarization and L-type calcium channel opening. The increased Ca^{2+} influx stimulates beta cell insulin release

https://t.me/USMLEWorldStep1

second-line agents; however, they are affordable and may be used as add-on therapy or as a replacement for metformin when cost is a major concern.

Sulfonylureas inhibit the ATP-sensitive potassium channel on the pancreatic beta cell membrane, inducing depolarization and L-type calcium channel opening. The increased Ca^{2+} influx stimulates beta cell **insulin release independent** of blood glucose concentrations (eg, even when blood glucose levels are normal or low). Therefore, a main associated risk is **hypoglycemia**. Circumstances that can lead to hypoglycemia include exercise, missed meals, or initiation of additional antidiabetic medications. Longer-acting sulfonylureas (eg, glyburide) are more prone to causing hypoglycemia than shorter-acting drugs (eg, glipizide) and are therefore not preferred.

(Choice A) Glucagon-like peptide-1 (GLP-1) helps regulate glucose by slowing gastric emptying and increasing insulin release in response to food intake. Pharmacologic GLP-1 agonists (eg, exenatide) lower blood glucose and promote weight loss; these agents are associated with acute pancreatitis.

(Choice B) In patients with poor oral intake (eg, gastroenteritis) or in those who are on concurrent diuretics (eg, furosemide), osmotic diuresis caused by sodium-glucose cotransporter 2 (SGLT2) inhibitors can lead to additional dehydration, resulting in acute kidney injury. In the long term, however, SGLT2 inhibitors have renoprotective effects and are recommended in patients with diabetic nephropathy.

(Choice D) Metformin can decrease absorption of vitamin B_{12}, leading to B_{12} deficiency in long-term use. Sulfonylureas do not have a significant effect on vitamin B_{12} metabolism.

(Choice E) SGLT2 inhibitors (eg, dapagliflozin) decrease renal reabsorption of glucose, leading to increased urinary glucose loss and lower blood glucose levels. The excess glucose in the urine can increase the risk of urinary tract infections and vulvovaginal candidiasis.

Educational objective:
Sulfonylureas inhibit the ATP-sensitive potassium channel on the pancreatic beta cell membrane, inducing depolarization and L-type calcium channel opening. The increased Ca^{2+} influx stimulates beta cell insulin release independent of blood glucose concentrations, increasing the risk of hypoglycemia when meals are missed or during exercise.

Pharmacology Endocrine, Diabetes & Metabolism Diabetes mellitus

https://t.me/USMLEWorldStep1

A 40-year-old woman is hospitalized due to a femoral neck fracture that occurred when she slipped while stepping out of the bathtub. The patient was diagnosed with a prolactinoma 3 years ago during evaluation of amenorrhea, but she refused medical or surgical treatments. The tumor is being monitored closely and has not increased in size or caused any visual symptoms. The patient has no other medical problems, takes no medications, and does not use tobacco, alcohol, or illicit drugs. She has 3 healthy children and no significant family history. The underlying mechanism for this patient's susceptibility to fracture is most likely to cause which of the following additional manifestations?

- A. Hand tremors
- B. Kidney stones
- C. Stomach ulcers
- D. Swallowing difficulty
- E. Vaginal dryness

Submit

https://t.me/USMLEWorldStep1

A 40-year-old woman is hospitalized due to a femoral neck fracture that occurred when she slipped while stepping out of the bathtub. The patient was diagnosed with a prolactinoma 3 years ago during evaluation of amenorrhea, but she refused medical or surgical treatments. The tumor is being monitored closely and has not increased in size or caused any visual symptoms. The patient has no other medical problems, takes no medications, and does not use tobacco, alcohol, or illicit drugs. She has 3 healthy children and no significant family history. The underlying mechanism for this patient's susceptibility to fracture is most likely to cause which of the following additional manifestations?

- A. Hand tremors (5%)
- ✕ B. Kidney stones (16%)
- C. Stomach ulcers (1%)
- D. Swallowing difficulty (0%)
- ✓ E. Vaginal dryness (75%)

Incorrect
Correct answer
E

75%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

Complications of prolactinoma	
Hyperprolactinemia	• **Premenopausal women:** Galactorrhea, estrogen deficiency (oligo/amenorrhea, decreased bone density, vaginal atrophy) • **Men:** Infertility, decreased libido, impotence • **Children/adolescents:** Delayed puberty, growth impairment
	• Headache

https://t.me/USMLEWorldStep1

Complications of prolactinoma	
Hyperprolactinemia	• **Premenopausal women:** Galactorrhea, estrogen deficiency (oligo/amenorrhea, decreased bone density, vaginal atrophy) • **Men:** Infertility, decreased libido, impotence • **Children/adolescents:** Delayed puberty, growth impairment
Mass-effect symptoms	• Headache • Visual field defects • Suppression of other pituitary hormones

Prolactinomas are the most common pituitary tumors. High levels of circulating prolactin, a hormone involved in milk production, result in galactorrhea (nonlactational milk production) and infertility in premenopausal women. Excess prolactin suppresses GnRH secretion from the hypothalamus, leading to reduced secretion of LH (and to a lesser extent FSH) and subsequent **hypogonadism**, anovulation, and amenorrhea. The resultant estrogen deficiency can manifest as vasomotor symptoms (eg, hot flashes), **vaginal dryness** and atrophy, and dyspareunia. Because estrogen maintains bone mass in premenopausal women, prolonged estrogen deficiency can lead to **osteoporosis** and an increased risk for fragility fractures (ie, fractures due to minimal trauma, such as a fall from standing height).

Men with prolactinomas may develop symptoms due to hypogonadism (eg, infertility, decreased libido), but galactorrhea is rare in both men and postmenopausal women as milk production requires estrogen/progesterone priming of the breast tissue. Men with prolactinomas are more likely to present at an advanced stage with **mass-effect symptoms** (eg, headache, visual field defects) due to compression of surrounding structures.

(Choices A and D) Central hyperthyroidism due to a TSH-secreting (thyrotroph) pituitary adenoma can present with weight loss, palpitations, systolic hypertension, and hyperadrenergic symptoms (eg, hand tremor). Chronic TSH stimulation can also lead to enlargement of the thyroid gland and compressive symptoms (eg, dysphagia). However, compression of thyrotroph cells by an enlarging prolactinoma causes central hypothyroidism.

(Choices B and C) Multiple endocrine neoplasia type 1 (MEN1) is characterized by primary hyperparathyroidism

https://t.me/USMLEWorldStep1

Prolactinomas are the most common pituitary tumors. High levels of circulating prolactin, a hormone involved in milk production, result in galactorrhea (nonlactational milk production) and infertility in premenopausal women. Excess prolactin suppresses GnRH secretion from the hypothalamus, leading to reduced secretion of LH (and to a lesser extent FSH) and subsequent **hypogonadism**, anovulation, and amenorrhea. The resultant estrogen deficiency can manifest as vasomotor symptoms (eg, hot flashes), **vaginal dryness** and atrophy, and dyspareunia. Because estrogen maintains bone mass in premenopausal women, prolonged estrogen deficiency can lead to **osteoporosis** and an increased risk for fragility fractures (ie, fractures due to minimal trauma, such as a fall from standing height).

Men with prolactinomas may develop symptoms due to hypogonadism (eg, infertility, decreased libido), but galactorrhea is rare in both men and postmenopausal women as milk production requires estrogen/progesterone priming of the breast tissue. Men with prolactinomas are more likely to present at an advanced stage with **mass-effect symptoms** (eg, headache, visual field defects) due to compression of surrounding structures.

(Choices A and D) Central hyperthyroidism due to a TSH-secreting (thyrotroph) pituitary adenoma can present with weight loss, palpitations, systolic hypertension, and hyperadrenergic symptoms (eg, hand tremor). Chronic TSH stimulation can also lead to enlargement of the thyroid gland and compressive symptoms (eg, dysphagia). However, compression of thyrotroph cells by an enlarging prolactinoma causes central hypothyroidism.

(Choices B and C) Multiple endocrine neoplasia type 1 (MEN1) is characterized by primary hyperparathyroidism (with hypercalcemia), pituitary tumors (including prolactinoma), and endocrine pancreatic tumors. Complications of hyperparathyroidism include osteoporosis and kidney stones. Stomach ulcers can occur in MEN1 due to hypercalcemia or a gastrin-producing pancreatic tumor (Zollinger-Ellison syndrome). However, most prolactinomas are sporadic and not associated with MEN1. In addition, MEN1 is rare, and this patient's lack of a significant family history makes it even less likely.

Educational objective:
In patients with prolactinoma, high levels of circulating prolactin suppress GnRH secretion from the hypothalamus, leading to reduced secretion of LH and subsequent hypogonadism, anovulation, and amenorrhea. The resulting estrogen deficiency can cause osteoporosis with an increased risk for fragility fractures, and lead to vaginal dryness and atrophy.

https://t.me/USMLEWorldStep1

Excess prolactin suppresses GnRH secretion from the hypothalamus, leading to reduced secretion of LH (and to a lesser extent FSH) and subsequent **hypogonadism**, anovulation, and amenorrhea. The resultant estrogen deficiency can manifest as vasomotor symptoms (eg, hot flashes), **vaginal dryness** and atrophy, and dyspareunia. Because estrogen maintains bone mass in premenopausal women, prolonged estrogen deficiency can lead to **osteoporosis** and an increased risk for fragility fractures (ie, fractures due to minimal trauma, such as a fall from standing height).

Men with prolactinomas may develop symptoms due to hypogonadism (eg, infertility, decreased libido), but galactorrhea is rare in both men and postmenopausal women as milk production requires estrogen/progesterone priming of the breast tissue. Men with prolactinomas are more likely to present at an advanced stage with **mass-effect symptoms** (eg, headache, visual field defects) due to compression of surrounding structures.

(Choices A and D) Central hyperthyroidism due to a TSH-secreting (thyrotroph) pituitary adenoma can present with weight loss, palpitations, systolic hypertension, and hyperadrenergic symptoms (eg, hand tremor). Chronic TSH stimulation can also lead to enlargement of the thyroid gland and compressive symptoms (eg, dysphagia). However, compression of thyrotroph cells by an enlarging prolactinoma causes central hypothyroidism.

(Choices B and C) Multiple endocrine neoplasia type 1 (MEN1) is characterized by primary hyperparathyroidism (with hypercalcemia), pituitary tumors (including prolactinoma), and endocrine pancreatic tumors. Complications of hyperparathyroidism include osteoporosis and kidney stones. Stomach ulcers can occur in MEN1 due to hypercalcemia or a gastrin-producing pancreatic tumor (Zollinger-Ellison syndrome). However, most prolactinomas are sporadic and not associated with MEN1. In addition, MEN1 is rare, and this patient's lack of a significant family history makes it even less likely.

Educational objective:
In patients with prolactinoma, high levels of circulating prolactin suppress GnRH secretion from the hypothalamus, leading to reduced secretion of LH and subsequent hypogonadism, anovulation, and amenorrhea. The resulting estrogen deficiency can cause osteoporosis with an increased risk for fragility fractures, and lead to vaginal dryness and atrophy.

References

- Hyperprolactinemia: pathophysiology and therapeutic approach.

https://t.me/USMLEWorldStep1

A 30-year-old woman comes to the office due to generalized weakness and paresthesia. Medical history is unremarkable, and she takes no medications. The patient mentions that her blood pressure was elevated at a workplace health fair 3 months ago; she attributed it to being "stressed out" and did not take any action. Blood pressure is 150/95 mm Hg. Cardiac examination is normal with full and symmetric distal pulses and no pedal edema. Laboratory evaluation shows low plasma renin activity and normal serum creatinine level. CT scan of the abdomen reveals a solitary, hypodense, 1.5-cm right adrenal mass. Which of the following patterns of serum electrolyte concentrations would most likely be seen in this patient?

	Bicarbonate	Potassium	Sodium
○ A.	High	Low	Low
○ B.	High	Low	Normal
○ C.	Low	High	Low
○ D.	Low	High	Normal
○ E.	Low	Low	High

Submit

https://t.me/USMLEWorldStep1

A 30-year-old woman comes to the office due to generalized weakness and paresthesia. Medical history is unremarkable, and she takes no medications. The patient mentions that her blood pressure was elevated at a workplace health fair 3 months ago; she attributed it to being "stressed out" and did not take any action. Blood pressure is 150/95 mm Hg. Cardiac examination is normal with full and symmetric distal pulses and no pedal edema. Laboratory evaluation shows low plasma renin activity and normal serum creatinine level. CT scan of the abdomen reveals a solitary, hypodense, 1.5-cm right adrenal mass. Which of the following patterns of serum electrolyte concentrations would most likely be seen in this patient?

	Bicarbonate	Potassium	Sodium	
✗ A.	High	Low	Low	(4%)
✓ B.	High	Low	Normal	(25%)
C.	Low	High	Low	(16%)
D.	Low	High	Normal	(4%)
E.	Low	Low	High	(49%)

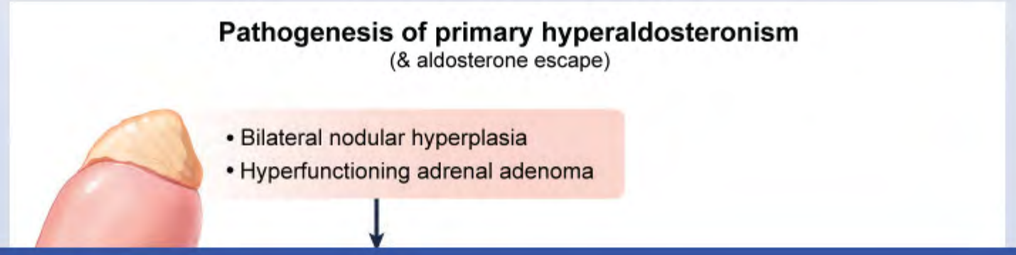
Incorrect
Correct answer
B

25%
Answered correctly

05 secs
Time Spent

2023
Version

Explanation

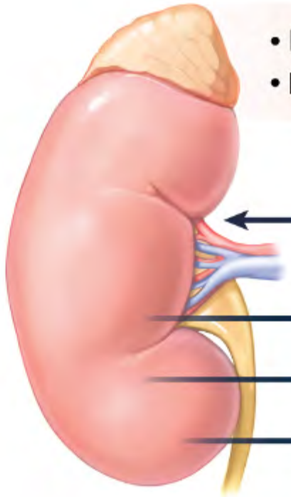


https://t.me/USMLEWorldStep1

D.	Low	High	Normal	(4%)

Exhibit Display

Pathogenesis of primary hyperaldosteronism
(& aldosterone escape)



- Bilateral nodular hyperplasia
- Hyperfunctioning adrenal adenoma

↓

↑ Aldosterone

- ↑ K^+ secretion → Hypokalemia
- ↑ H^+ secretion → Metabolic alkalosis
- ↑ Na^+ reabsorption → Hypertension (↑ Blood volume) → ↓ Renin, ↓ Angiotensin II

Aldosterone escape
- Limits edema

↑ Renal blood flow
↑ Glomerular filtration rate → ↑ Na^+ excretion
↑ Atrial natriuretic peptide

©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

This patient's onset of **hypertension** at a young age suggests a **secondary** cause. The weakness and paresthesia indicate an associated electrolyte or acid-base disturbance. These findings, along with suppressed

https://t.me/USMLEWorldStep1

This patient's onset of **hypertension** at a young age suggests a **secondary** cause. The weakness and paresthesia indicate an associated electrolyte or acid-base disturbance. These findings, along with suppressed plasma renin, suggest **primary hyperaldosteronism** (ie, mineralocorticoid excess). Primary hyperaldosteronism is most commonly caused by a unilateral **adrenal adenoma** (Conn syndrome) or bilateral adrenal hyperplasia (idiopathic hyperaldosteronism).

Hyperaldosteronism is characterized by increased distal Na^+ reabsorption in the renal collecting ducts. This creates a negative charge in the lumen, pulling H^+ and K^+ from tubular cells and leading to their urinary excretion. As a result, **hypokalemia** is common. Increased H^+ excretion by alpha-intercalated cells promotes bicarbonate production and increased activity of the basolateral HCO_3^-/Cl^- exchanger, resulting in elevated serum bicarbonate and **metabolic alkalosis (Choice E)**.

Despite increased Na^+ reabsorption, overt volume overload (eg, pedal edema) is rarely seen due to a phenomenon known as **aldosterone escape**. Increased intravascular volume increases pressure natriuresis and augments atrial natriuretic peptide release, thereby limiting net sodium retention and overt volume overload. Hypernatremia is also not typically seen because the temporary increase in serum osmolality triggers a compensatory rise in antidiuretic hormone (ADH) release.

(Choice A) Loop or thiazide diuretic use can cause metabolic alkalosis, hypokalemia, and hyponatremia (mostly with thiazides) due to urinary losses of H^+, K^+, and Na^+. Na^+ loss leads to hypovolemia, which can exacerbate hyponatremia (due to nonosmotic stimulus for ADH secretion) and alkalosis (due to increased bicarbonate reabsorption).

(Choice C) Primary adrenal insufficiency reduces urinary excretion of H^+ and K^+ and promotes renal Na^+ loss due to low aldosterone. As a result, metabolic acidosis, hyperkalemia, hyponatremia, and hypovolemia develop.

(Choice D) Mineralocorticoid receptor antagonists (eg, spironolactone) block aldosterone receptors, thereby impairing urinary excretion of H^+ and K^+. Common adverse effects therefore include metabolic acidosis and hyperkalemia. Na^+ excretion is only mildly increased, and serum Na^+ concentration is usually not significantly affected.

Educational objective:

https://t.me/USMLEWorldStep1

creates a negative charge in the lumen, pulling H^+ and K^+ from tubular cells and leading to their urinary excretion. As a result, **hypokalemia** is common. Increased H^+ excretion by alpha-intercalated cells promotes bicarbonate production and increased activity of the basolateral HCO_3^-/Cl^- exchanger, resulting in elevated serum bicarbonate and **metabolic alkalosis (Choice E)**.

Despite increased Na^+ reabsorption, overt volume overload (eg, pedal edema) is rarely seen due to a phenomenon known as **aldosterone escape**. Increased intravascular volume increases pressure natriuresis and augments atrial natriuretic peptide release, thereby limiting net sodium retention and overt volume overload. Hypernatremia is also not typically seen because the temporary increase in serum osmolality triggers a compensatory rise in antidiuretic hormone (ADH) release.

(Choice A) Loop or thiazide diuretic use can cause metabolic alkalosis, hypokalemia, and hyponatremia (mostly with thiazides) due to urinary losses of H^+, K^+, and Na^+. Na^+ loss leads to hypovolemia, which can exacerbate hyponatremia (due to nonosmotic stimulus for ADH secretion) and alkalosis (due to increased bicarbonate reabsorption).

(Choice C) Primary adrenal insufficiency reduces urinary excretion of H^+ and K^+ and promotes renal Na^+ loss due to low aldosterone. As a result, metabolic acidosis, hyperkalemia, hyponatremia, and hypovolemia develop.

(Choice D) Mineralocorticoid receptor antagonists (eg, spironolactone) block aldosterone receptors, thereby impairing urinary excretion of H^+ and K^+. Common adverse effects therefore include metabolic acidosis and hyperkalemia. Na^+ excretion is only mildly increased, and serum Na^+ concentration is usually not significantly affected.

Educational objective:
Primary hyperaldosteronism increases distal Na^+ reabsorption (secondary hypertension), leading to increased urinary excretion of H^+ and K^+ (metabolic alkalosis and hypokalemia). Overt volume overload is not seen due to aldosterone escape, and serum Na^+ concentration is typically normal due to preserved antidiuretic hormone function.

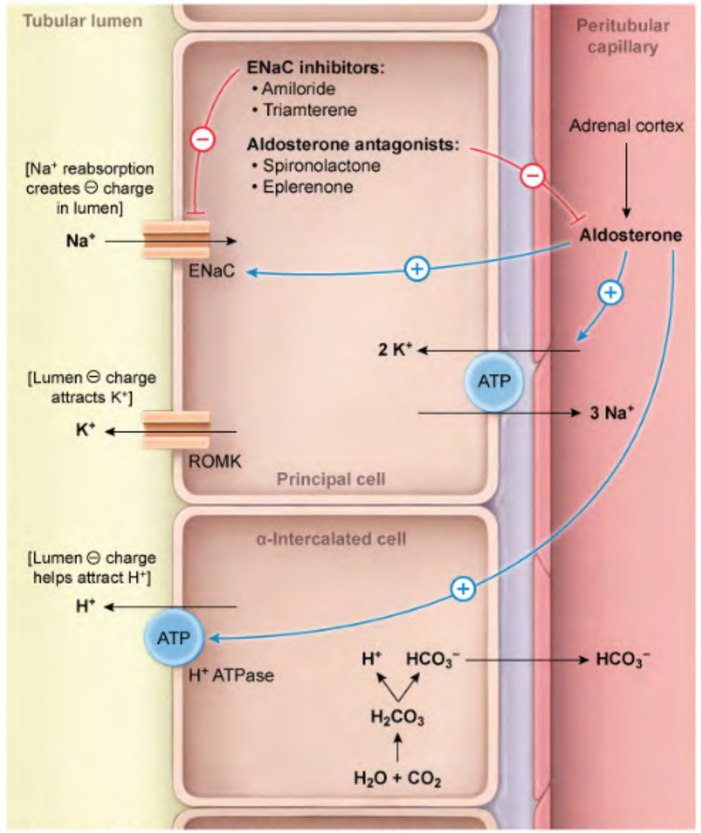
Pathophysiology Endocrine, Diabetes & Metabolism Hyperaldosteronism

https://t.me/USMLEWorldStep1

↑Na⁺ reabsorption → Hypertension (↑Blood volume) → ↓Renin ↓Angiotensin II

Exhibit Display

Action of aldosterone in the collecting duct of the nephron



ENaC = epithelial sodium channel; **ROMK** = renal outer medullary potassium channel. ©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

This p
parest
plasm
is mos
(idiopa

Hyper
create
As a r
produc
and **m**

Despit
known
atrial r
is also
antidiu

(Choi
with th
hypon
reabsorption).

(Choice C) Primary adrenal insufficiency reduces urinary excretion of H^+ and K^+ and promotes renal Na^+ loss due

https://t.me/USMLEWorldStep1

A 16-year-old girl is brought to the office by her mother due to concern about excessive weight loss. The patient has lost 4.5 kg (10 lb) over the past 2 months, but thinks she still appears overweight, and is worried about gaining weight. She does not use tobacco, alcohol, or illicit drugs. Her mother has hypothyroidism. Blood pressure is 130/70 mm Hg, and pulse is 105/min and regular. There are no orthostatic changes. BMI is 22 kg/m^2. On examination, the patient appears anxious. The thyroid is small and without palpable nodules. There is a fine tremor seen in the fingers when the arms are outstretched. Deep tendon reflexes are 3+ diffusely. The skin is warm and moist. Laboratory results show decreased TSH, elevated free thyroxine (T4), and undetectable thyroglobulin levels. Which of the following is most likely to be seen on thyroid biopsy of this patient?

- A. Diffuse atrophy of the thyroid follicles with decreased colloid
- B. Extensive lymphocytic infiltrate with germinal center formation
- C. Inflammatory disruption of the follicles and multinucleated giant cells
- D. Small clusters of spindle cells and foci of C-cell hyperplasia
- E. Tall columnar follicular epithelium with scalloped margins of the colloid

Submit

https://t.me/USMLEWorldStep1

A 16-year-old girl is brought to the office by her mother due to concern about excessive weight loss. The patient has lost 4.5 kg (10 lb) over the past 2 months, but thinks she still appears overweight, and is worried about gaining weight. She does not use tobacco, alcohol, or illicit drugs. Her mother has hypothyroidism. Blood pressure is 130/70 mm Hg, and pulse is 105/min and regular. There are no orthostatic changes. BMI is 22 kg/m^2. On examination, the patient appears anxious. The thyroid is small and without palpable nodules. There is a fine tremor seen in the fingers when the arms are outstretched. Deep tendon reflexes are 3+ diffusely. The skin is warm and moist. Laboratory results show decreased TSH, elevated free thyroxine (T4), and undetectable thyroglobulin levels. Which of the following is most likely to be seen on thyroid biopsy of this patient?

- ✓ A. Diffuse atrophy of the thyroid follicles with decreased colloid (47%)
- ✗ B. Extensive lymphocytic infiltrate with germinal center formation (14%)
- C. Inflammatory disruption of the follicles and multinucleated giant cells (7%)
- D. Small clusters of spindle cells and foci of C-cell hyperplasia (4%)
- E. Tall columnar follicular epithelium with scalloped margins of the colloid (27%)

Incorrect
Correct answer
A

47%
Answered correctly

04 secs
Time Spent

2023
Version

Explanation

This patient's symptoms (eg, weight loss, tachycardia, and tremors), elevated free thyroxine (T4), and suppressed TSH are indicative of **thyrotoxicosis**. However, her thyroid is small and serum **thyroglobulin is undetectable**, which suggests an **exogenous source** of thyroid hormone. Thyroglobulin is a glycoprotein produced by thyroid follicular cells that makes up a substantial component of follicular colloid and serves as the substrate for the formation of thyroid hormone. A small amount is released by the thyroid in normal function. Low levels, as in this patient, suggest noninflammatory **suppression of thyroid activity**.

https://t.me/USMLEWorldStep1

This patient's symptoms (eg, weight loss, tachycardia, and tremors), elevated free thyroxine (T4), and suppressed TSH are indicative of **thyrotoxicosis**. However, her thyroid is small and serum **thyroglobulin is undetectable**, which suggests an **exogenous source** of thyroid hormone. Thyroglobulin is a glycoprotein produced by thyroid follicular cells that makes up a substantial component of follicular colloid and serves as the substrate for the formation of thyroid hormone. A small amount is released by the thyroid in normal function. Low levels, as in this patient, suggest noninflammatory **suppression of thyroid activity**.

In light of her mother's hypothyroidism, which suggests a possible source of levothyroxine tablets, this patient is likely surreptitiously taking thyroid hormone in an attempt to lose weight. Exogenous thyrotoxicosis can also occur in patients taking over-the-counter supplements containing animal thyroid tissue and in erroneous dosing of thyroid replacement therapy. Excess T4 supplementation suppresses TSH, which decreases iodine organification and colloid formation resulting in **atrophy of thyroid follicles**.

(Choice B) Histopathology in chronic autoimmune (Hashimoto) thyroiditis is characterized by a mononuclear infiltrate consisting of lymphocytes and plasma cells, often with germinal centers. Hashimoto thyroiditis typically presents with primary hypothyroidism (elevated TSH, low free T4) and goiter; although Hashimoto's can occasionally present with an initial hyperthyroid phase, these patients will have elevated thyroglobulin levels due to inflammatory disruption of thyroid follicles.

(Choice C) Subacute granulomatous (de Quervain) thyroiditis is characterized by disruption of follicles and a mixed cellular infiltrate with occasional multinucleated giant cells. Patients may have hyperthyroidism but typically have a painful, tender thyroid gland and high levels of thyroglobulin due to destructive thyroiditis.

(Choice D) Medullary thyroid cancer is a neuroendocrine tumor that arises from calcitonin-secreting parafollicular C cells. Microscopy shows nests or sheets of polygonal or spindle-shaped cells with extracellular amyloid deposits (derived from calcitonin). Clinical features include diarrhea, flushing, and thyroid nodules, but TSH and free T4 are normal.

(Choice E) Graves disease presents with a diffusely enlarged thyroid gland associated with hyperthyroidism, exophthalmos, and pretibial myxedema. The thyroid follicular epithelium is tall and crowded with hyperactive reabsorption, causing scalloping around the edges of the colloid. However, high serum levels of thyroglobulin

https://t.me/USMLEWorldStep1

In light of her mother's hypothyroidism, which suggests a possible source of levothyroxine tablets, this patient is likely surreptitiously taking thyroid hormone in an attempt to lose weight. Exogenous thyrotoxicosis can also occur in patients taking over-the-counter supplements containing animal thyroid tissue and in erroneous dosing of thyroid replacement therapy. Excess T4 supplementation suppresses TSH, which decreases iodine organification and colloid formation resulting in **atrophy of thyroid follicles**.

(Choice B) Histopathology in chronic autoimmune (Hashimoto) thyroiditis is characterized by a mononuclear infiltrate consisting of lymphocytes and plasma cells, often with germinal centers. Hashimoto thyroiditis typically presents with primary hypothyroidism (elevated TSH, low free T4) and goiter; although Hashimoto's can occasionally present with an initial hyperthyroid phase, these patients will have elevated thyroglobulin levels due to inflammatory disruption of thyroid follicles.

(Choice C) Subacute granulomatous (de Quervain) thyroiditis is characterized by disruption of follicles and a mixed cellular infiltrate with occasional multinucleated giant cells. Patients may have hyperthyroidism but typically have a painful, tender thyroid gland and high levels of thyroglobulin due to destructive thyroiditis.

(Choice D) Medullary thyroid cancer is a neuroendocrine tumor that arises from calcitonin-secreting parafollicular C cells. Microscopy shows nests or sheets of polygonal or spindle-shaped cells with extracellular amyloid deposits (derived from calcitonin). Clinical features include diarrhea, flushing, and thyroid nodules, but TSH and free T4 are normal.

(Choice E) Graves disease presents with a diffusely enlarged thyroid gland associated with hyperthyroidism, exophthalmos, and pretibial myxedema. The thyroid follicular epithelium is tall and crowded with hyperactive reabsorption, causing scalloping around the edges of the colloid. However, high serum levels of thyroglobulin would be seen due to increased thyroid metabolic activity.

Educational objective:
Exogenous hyperthyroidism is characterized by elevated free thyroxine (T4), suppressed TSH, and low/undetectable thyroglobulin. It can occur with surreptitious levothyroxine misuse, animal-sourced thyroid supplements, and erroneous dosing of thyroid replacement therapy. Over time, the lack of TSH stimulation causes the thyroid follicles to become atrophic.

https://t.me/USMLEWorldStep1

This patient's symptoms (eg, weight loss, tachycardia, and tremors), elevated free thyroxine (T4), and suppressed TSH a
which
follicul
format
patien

In ligh
likely s
in pati
replac
colloid

(Choi
infiltrat
preser
occasi
inflam

(Choi
mixed
have a

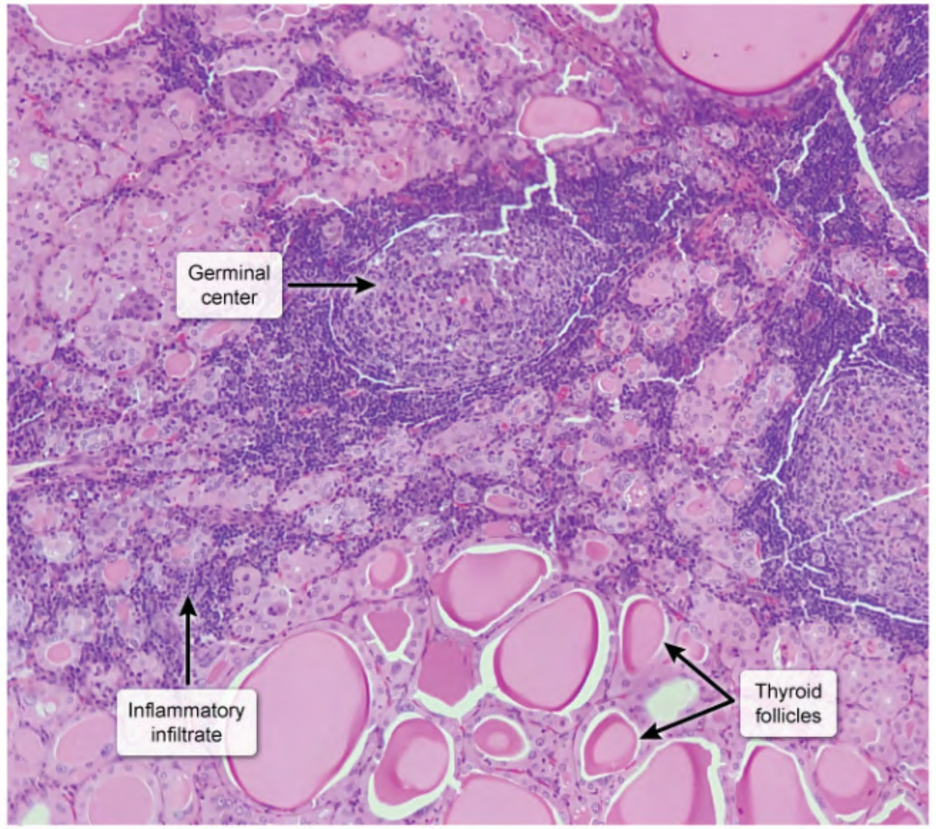
(Choi
C cells
(derive
norma

(Choi
exoph

reabsorption, causing scalloping around the edges of the colloid. However, high serum levels of thyroglobulin

Exhibit Display

Hashimoto thyroiditis



©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

This patient's symptoms (eg, weight loss, tachycardia, and tremors), elevated free thyroxine (T4), and suppressed TSH a
which
follicul
format
patien

In ligh
likely s
in pati
replac
colloid

(Choi
infiltrat
preser
occasi
inflam

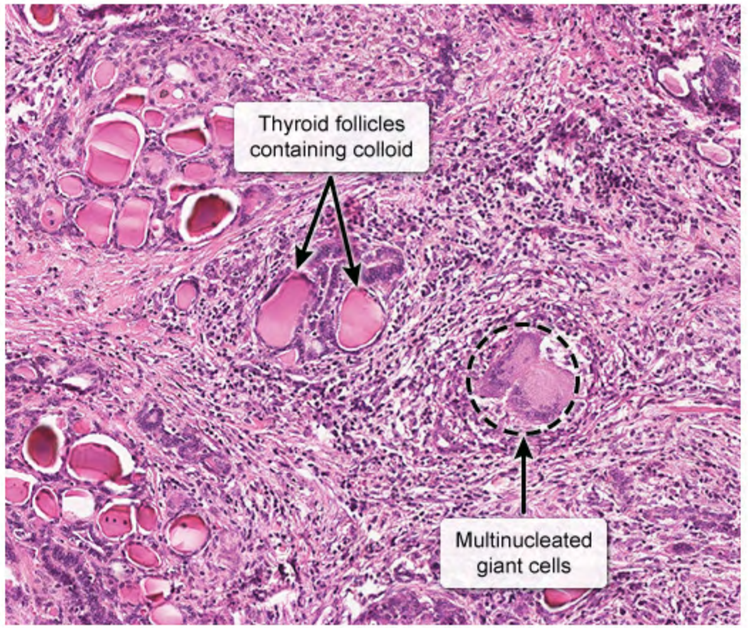
(Choi
mixed
have a

(Choi
C cells
(derive
norma

(Choi
exoph
reabsorption, causing scalloping around the edges of the colloid. However, high serum levels of thyroglobulin

Exhibit Display

Granulomatous (de Quervain) thyroiditis



©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

follicular cells that makes up a substantial component of follicular colloid and serves as the substrate for the

format

patien

In ligh

likely s

in pati

replac

colloid

(Choi

infiltra

preser

occasi

inflam

(Choi

mixed

have a

(Choi

C cells

(derive

norma

(Choi

exoph

reabs

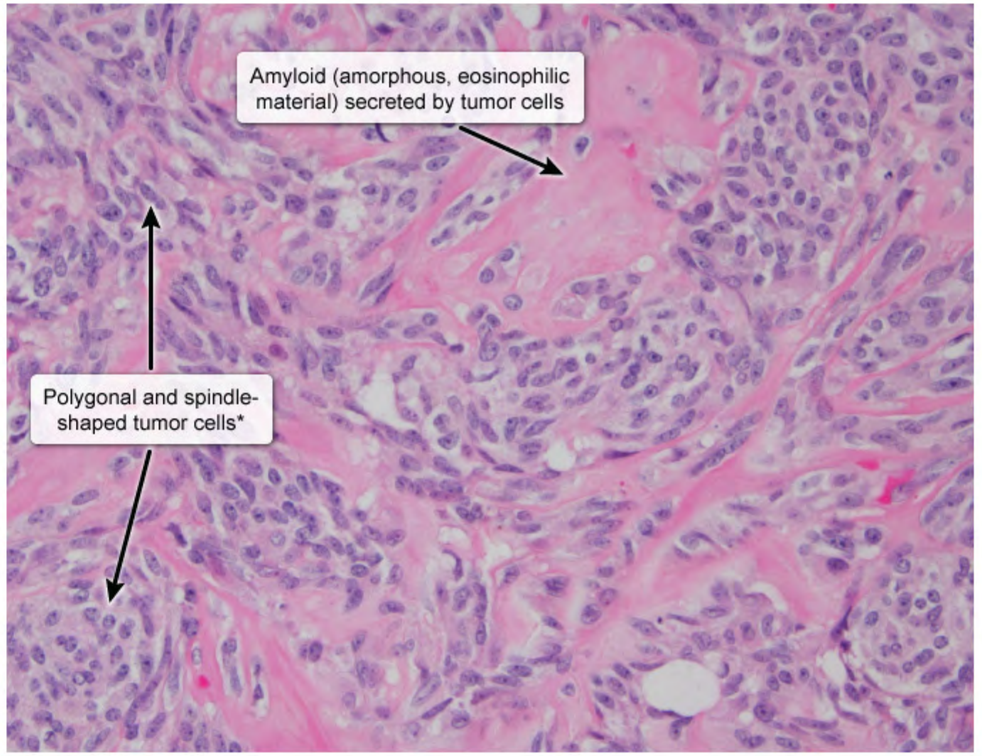
would

Educa

Exogenous hyperthyroidism is characterized by elevated free thyroxine (T4), suppressed TSH, and

Exhibit Display

Medullary thyroid carcinoma



*Derived from C (parafollicular) cells.

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

follicular cells that makes up a substantial component of follicular colloid and serves as the substrate for the

format

patien

In ligh

likely s

in pati

replac

colloid

(Choi

infiltrat

preser

occasi

inflam

(Choi

mixed

have a

(Choi

C cells

(derive

norma

(Choi

exoph

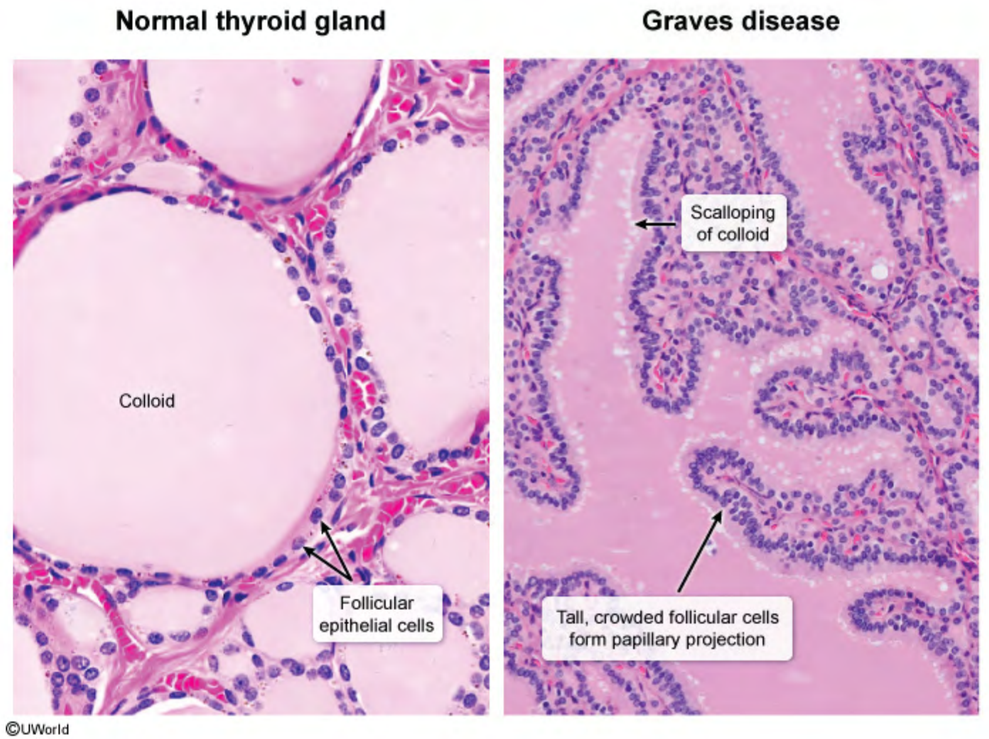
reabs

would

Educa

Exogenous hyperthyroidism is characterized by elevated free thyroxine (T4), suppressed TSH, and

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

In a series of animal experiments, the insulin concentration in the pancreatic veins is measured after the administration of various agents. Epinephrine administration is found to cause a decrease in insulin levels. However, after pretreatment with Drug A, epinephrine injection causes a paradoxical increase in insulin concentration. Which of the following receptors does Drug A most likely block?

- A. Alpha-2 adrenergic receptors
- B. Beta-2 adrenergic receptors
- C. Glucagon-like peptide-1 receptors
- D. Histamine H2 receptors
- E. Muscarinic M3 receptors

Submit

https://t.me/USMLEWorldStep1

In a series of animal experiments, the insulin concentration in the pancreatic veins is measured after the administration of various agents. Epinephrine administration is found to cause a decrease in insulin levels. However, after pretreatment with Drug A, epinephrine injection causes a paradoxical increase in insulin concentration. Which of the following receptors does Drug A most likely block?

- ✓ A. Alpha-2 adrenergic receptors (41%)
- ✗ B. Beta-2 adrenergic receptors (37%)
- C. Glucagon-like peptide-1 receptors (18%)
- D. Histamine H2 receptors (0%)
- E. Muscarinic M3 receptors (1%)

Incorrect
Correct answer
A

41%
Answered correctly

04 secs
Time Spent

2023
Version

Explanation

G protein-coupled receptors on pancreatic beta cells

Receptor	G alpha subunit	Insulin secretion
Muscarinic M3	G_q	↑
Glucagon	G_s/ G_q	
• Beta-2 adrenergic • Glucagon-like peptide-1	G_s	
• Alpha-2 adrenergic • Somatostatin 2	G_i	↓

©USMLEWorld LLC

https://t.me/USMLEWorldStep1

E. Muscarinic M3 receptors (1%)

Exhibit Display

G protein-coupled receptors on pancreatic beta cells

Receptor	G alpha subunit	Insulin secretion
Muscarinic M3	G_q	↑
Glucagon	G_s/ G_q	
• Beta-2 adrenergic • Glucagon-like peptide-1	G_s	
• Alpha-2 adrenergic • Somatostatin 2	G_i	↓

©USMLEWorld, LLC

Zoom In Zoom Out Reset New | Existing My Notebook

Pancre
nervou
induce
and be
beta-2
Howev
inhibiti
but the
receptor blocker (Drug A), epinephrine's effect on beta-2 receptors would become dominant, resulting in increased

https://t.me/USMLEWorldStep1

• Alpha-2 adrenergic • Somatostatin 2	G_i	↓

©USMLEWorld, LLC

Pancreatic beta cell insulin secretion is influenced by serum glucose levels and other factors such as autonomic nervous system activity. Parasympathetic stimulation of muscarinic M3 receptors promotes insulin secretion and is induced by the smell and/or sight of food. In contrast, sympathetic stimulation is more complex, since both alpha-2 and beta-2 adrenergic receptors are present on pancreatic beta cells and exert opposite effects. Stimulation of beta-2 receptors promotes insulin secretion while stimulation of alpha-2 receptors inhibits insulin release. However, the alpha-2-mediated inhibitory effect is predominant, causing sympathetic stimulation to lead to overall inhibition of insulin secretion. Likewise, epinephrine administration activates both alpha-2 and beta-2 receptors, but the overriding inhibitory effect results in decreased insulin secretion. Following pretreatment with an alpha-2 receptor blocker (Drug A), epinephrine's effect on beta-2 receptors would become dominant, resulting in increased insulin secretion.

(Choice B) Stimulation of beta-2 adrenergic receptors results in increased insulin secretion; beta-2 receptor blockade would inhibit insulin release.

(Choice C) Glucagon-like peptide-1 (GLP-1) is an incretin hormone secreted by the intestinal L cells in response to food and acts on receptors found on pancreatic beta cells to potentiate glucose-induced insulin release. Blocking GLP-1 receptors reduces insulin release. GLP-1 receptor agonists (eg, exenatide, liraglutide) are commonly used to treat type 2 diabetes mellitus.

(Choice D) Histamine H2 receptor stimulation increases insulin secretion. Blocking these receptors would cause a decrease in insulin release.

(Choice E) Parasympathetic stimulation increases insulin secretion via M3 muscarinic receptors. Blocking these receptors would inhibit the release of insulin.

Educational objective:
Alpha-2 adrenergic receptors inhibit insulin secretion, and beta-2 adrenergic receptors stimulate insulin secretion. The alpha-2-mediated inhibitory effect is generally predominant, causing sympathetic stimulation to lead to overall inhibition of insulin secretion.

https://t.me/USMLEWorldStep1

A 21-year-old man comes to the emergency department due to several days of dizziness and extreme fatigue. The patient has been drinking a lot of water and urinating more than usual for the past 2 weeks. He developed nausea and vomiting one day ago and has had difficulty keeping food and liquids down. The patient has no other medical conditions and takes no medications. Blood pressure is 90/60 mm Hg, pulse is 120/min, and respirations are 20/min. Urinalysis is positive for glucose and ketones. The patient is given intravenous fluids and an intravenous infusion of recombinant human insulin without any structural modifications. His condition improves, and he remains stable for the rest of the hospitalization. In preparation for discharge, a plan is made to prescribe a regimen that includes a subcutaneous formulation of the same insulin that the patient was receiving intravenously. Which of the following drug concentration curves shown in the image below is most likely to be obtained after subcutaneous injection of this insulin?

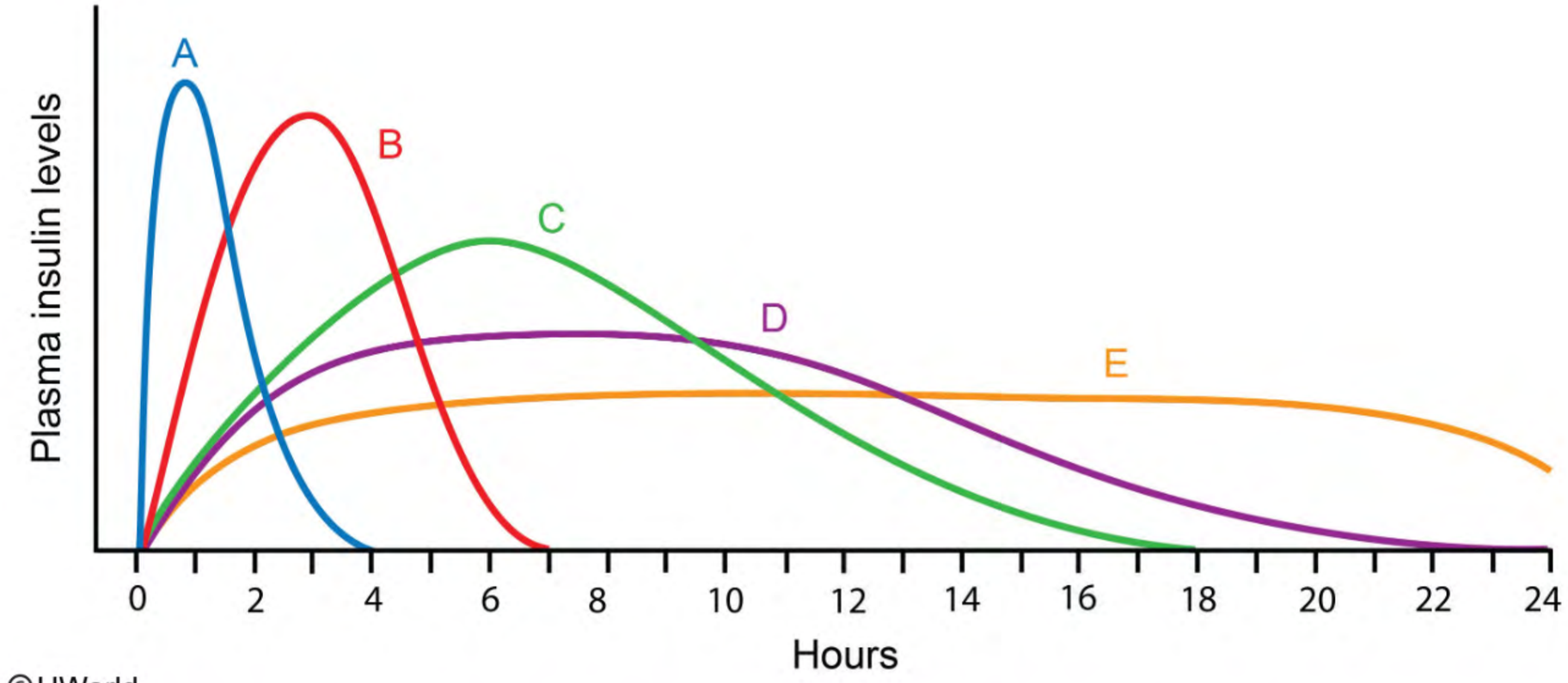
- A. A
- B. B
- C. C
- D. D
- E. E

Submit

https://t.me/USMLEWorldStep1

A 21-year-old man comes to the emergency department due to several days of dizziness and extreme fatigue. The patien
and vo
conditi
20/mir
infusio
remair
regime
Which
subcut

Exhibit Display

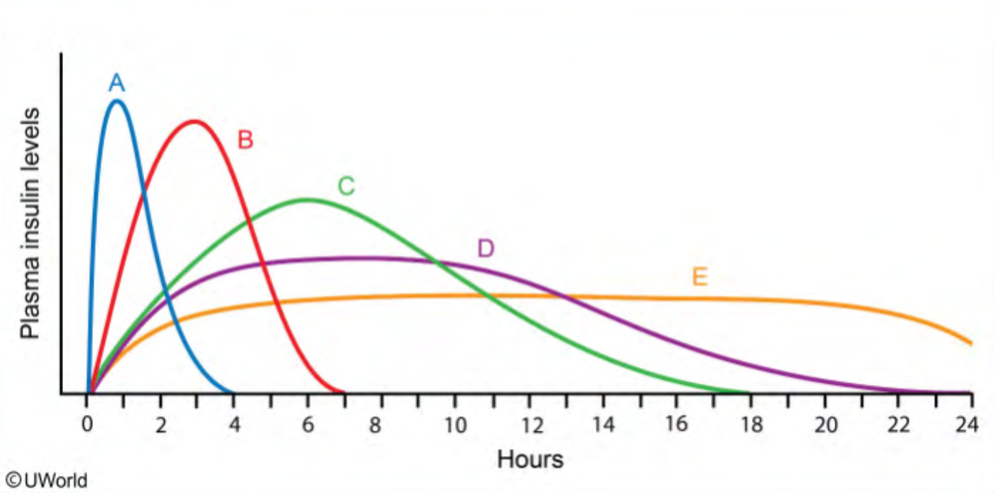


Zoom In Zoom Out Reset New | Existing My Notebook

D. D

https://t.me/USMLEWorldStep1

conditions and takes no medications. Blood pressure is 90/60 mm Hg, pulse is 120/min, and respirations are 20/min. Urinalysis is positive for glucose and ketones. The patient is given intravenous fluids and an intravenous infusion of recombinant human insulin without any structural modifications. His condition improves, and he remains stable for the rest of the hospitalization. In preparation for discharge, a plan is made to prescribe a regimen that includes a subcutaneous formulation of the same insulin that the patient was receiving intravenously. Which of the following drug concentration curves shown in the image below is most likely to be obtained after subcutaneous injection of this insulin?



- A. A (12%)
- ✓ B. B (42%)
- ✗ C. C (24%)
- D. D (8%)
- E. E (12%)

Incorrect
Correct answer
B

42%
Answered correctly

09 secs
Time Spent

2023
Version

https://t.me/USMLEWorldStep1

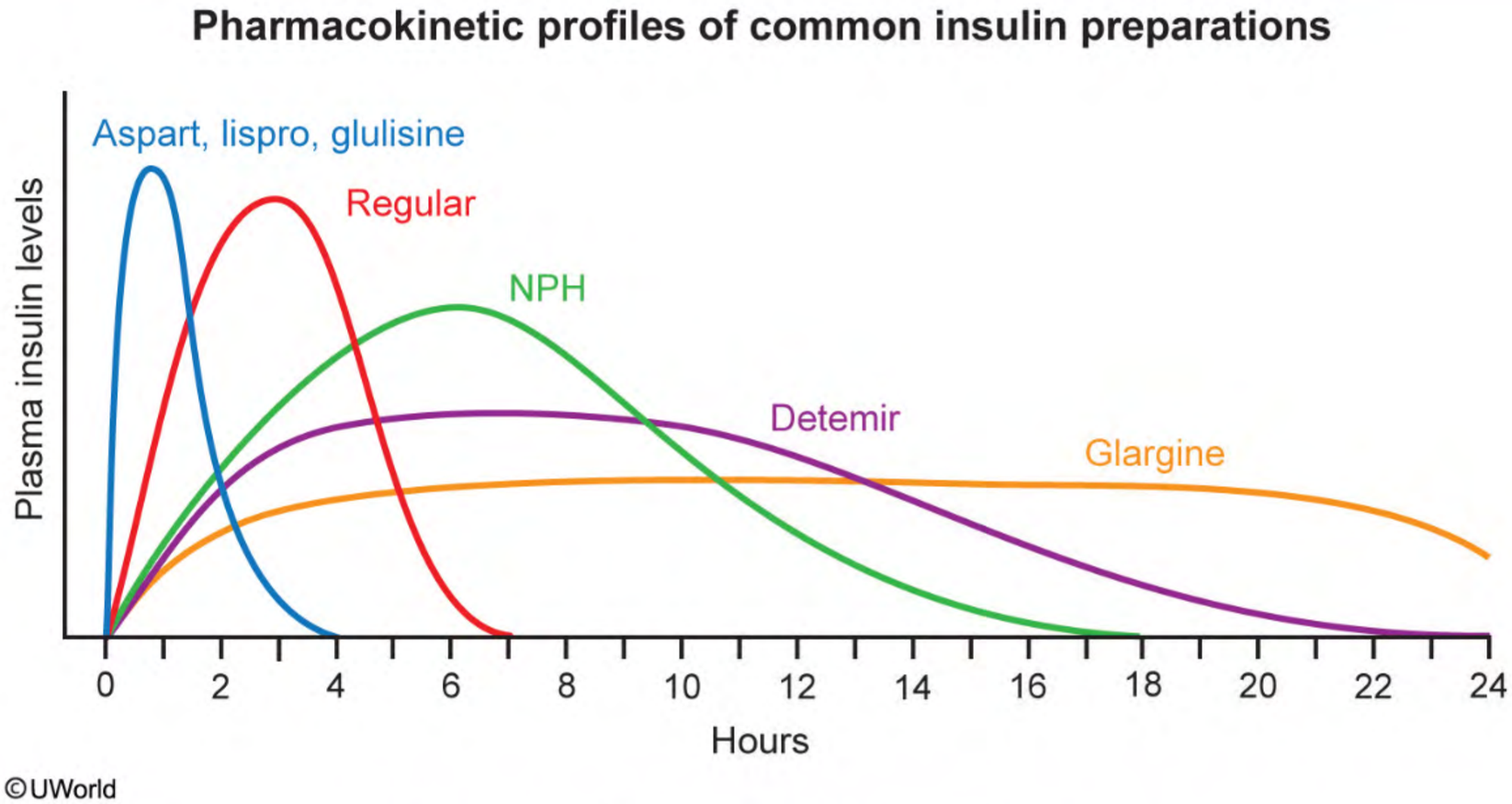
Incorrect
Correct answer
B

42%
Answered correctly

09 secs
Time Spent

2023
Version

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

This y
glucos
is trea
within
rate, w

Follow
patien
within
duration of action compared to the intravenous formation are due to subcutaneous polymerization (eg, hexamer formation) that delays systemic absorption.

https://t.me/USMLEWorldStep1

Hours

©UWorld

This young patient with symptoms of hyperglycemia (eg, polyuria, polydipsia) that progressed to volume depletion, glucosuria, and ketonuria has **diabetic ketoacidosis** (DKA), likely due to new-onset type 1 diabetes mellitus. DKA is treated with an **intravenous** infusion of **regular insulin** that begins to lower serum glucose and ketone levels within **minutes**. Intravenous regular insulin has a half-life of 5 minutes, allowing rapid adjustment of the infusion rate, which is required when glucose levels change rapidly during DKA management.

Following resolution of DKA, patients are transitioned to subcutaneous insulin to be continued at home. This patient's postdischarge regimen includes the **subcutaneous** formulation of regular insulin, which begins working within 30 minutes after injection, **peaks in 2-4 hours**, and lasts 5-8 hours. The delayed onset and prolonged duration of action compared to the intravenous formation are due to subcutaneous polymerization (eg, hexamer formation) that delays systemic absorption.

Subcutaneous regular insulin is used to treat **post prandial hyperglycemia** and is used with basal insulin (intermediate acting [ie, NPH] or long acting [eg, glargine]), which treats fasting hyperglycemia. Regular insulin and neutral protamine Hagedorn (NPH) are the only human recombinant insulins **without amino acid modification**. All other insulin preparations (eg, glargine, lispro) have structural modifications (eg, amino acid changes) to improve pharmacokinetics and are considered insulin analogs.

(Choice A) Insulin aspart, lispro, and glulisine are rapid-acting insulin analogues used to treat postprandial hyperglycemia. Because they have a more rapid onset of action (15 min) and peak effect (45-75 min) compared to regular insulin, these analogues more closely mimic postprandial physiologic insulin secretion.

(Choice C) NPH is an intermediate-acting insulin that has a more delayed onset (2 hr) and peak effect (4-6 hr) compared to regular insulin; it can be used as a basal insulin (given twice a day). Unlike regular insulin, NPH is a crystalline suspension that is not suitable for intravenous use.

(Choices D and E) Detemir and glargine are long-acting basal insulin analogues that do not have a significant peak effect. Unlike glargine, which has a duration of action of 24 hours, detemir typically lasts just under 24 hours, making it the less-preferred basal insulin.

Educational objective:

https://t.me/USMLEWorldStep1

Following resolution of DKA, patients are transitioned to subcutaneous insulin to be continued at home. This patient's postdischarge regimen includes the **subcutaneous** formulation of regular insulin, which begins working within 30 minutes after injection, **peaks in 2-4 hours**, and lasts 5-8 hours. The delayed onset and prolonged duration of action compared to the intravenous formation are due to subcutaneous polymerization (eg, hexamer formation) that delays systemic absorption.

Subcutaneous regular insulin is used to treat **post prandial hyperglycemia** and is used with basal insulin (intermediate acting [ie, NPH] or long acting [eg, glargine]), which treats fasting hyperglycemia. Regular insulin and neutral protamine Hagedorn (NPH) are the only human recombinant insulins **without amino acid modification**. All other insulin preparations (eg, glargine, lispro) have structural modifications (eg, amino acid changes) to improve pharmacokinetics and are considered insulin analogs.

(Choice A) Insulin aspart, lispro, and glulisine are rapid-acting insulin analogues used to treat postprandial hyperglycemia. Because they have a more rapid onset of action (15 min) and peak effect (45-75 min) compared to regular insulin, these analogues more closely mimic postprandial physiologic insulin secretion.

(Choice C) NPH is an intermediate-acting insulin that has a more delayed onset (2 hr) and peak effect (4-6 hr) compared to regular insulin; it can be used as a basal insulin (given twice a day). Unlike regular insulin, NPH is a crystalline suspension that is not suitable for intravenous use.

(Choices D and E) Detemir and glargine are long-acting basal insulin analogues that do not have a significant peak effect. Unlike glargine, which has a duration of action of 24 hours, detemir typically lasts just under 24 hours, making it the less-preferred basal insulin.

Educational objective:
Intravenous regular insulin has a rapid onset and short half-life, allowing the rapid adjustments needed in diabetic ketoacidosis management. In contrast, regular insulin given subcutaneously starts working within 30 minutes, peaks in 2-4 hours, and lasts 5-8 hours, making it usable as a premeal insulin that treats postprandial hyperglycemia.

References

- New insulin preparations: a primer for the clinician.

https://t.me/USMLEWorldStep1

A 34-year-old woman comes to the office with progressive weight gain over the past year. She also has weakness, easy bruising, and irregular menstrual periods. The patient takes no medications and has no drug allergies. Blood pressure is 150/90 mm Hg and pulse is 78/min. Laboratory studies reveal an elevated serum cortisol level that is not suppressed following administration of low-dose dexamethasone. Her 24-hour urine free-cortisol concentration and plasma ACTH are elevated. Which of the following histopathologic findings are most likely to be present in this patient's adrenal glands?

- A. Adenoma of the zona glomerulosa
- B. Atrophy of all layers of the adrenal cortex
- C. Hyperplasia of the adrenal medulla
- D. Hyperplasia of the zona fasciculata and reticularis
- E. Neoplasia of adrenal medulla

Submit

https://t.me/USMLEWorldStep1

A 34-year-old woman comes to the office with progressive weight gain over the past year. She also has weakness, easy bruising, and irregular menstrual periods. The patient takes no medications and has no drug allergies. Blood pressure is 150/90 mm Hg and pulse is 78/min. Laboratory studies reveal an elevated serum cortisol level that is not suppressed following administration of low-dose dexamethasone. Her 24-hour urine free-cortisol concentration and plasma ACTH are elevated. Which of the following histopathologic findings are most likely to be present in this patient's adrenal glands?

- A. Adenoma of the zona glomerulosa (6%)
- ✗ B. Atrophy of all layers of the adrenal cortex (8%)
- C. Hyperplasia of the adrenal medulla (3%)
- ✓ D. Hyperplasia of the zona fasciculata and reticularis (80%)
- E. Neoplasia of adrenal medulla (1%)

Incorrect
Correct answer
D

80%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

Common causes of Cushing syndrome		
	Etiology	**Pathologic findings**
ACTH-dependent	Cushing disease (ie, pituitary ACTH hypersecretion)	• Bilateral hyperplasia involving the zona fasciculata & reticularis
	Ectopic ACTH syndrome (eg, paraneoplastic ACTH secretion)	
		• Benign tumors are typically round, well

https://t.me/USMLEWorldStep1

Common causes of Cushing syndrome		
	Etiology	**Pathologic findings**
ACTH-dependent	Cushing disease (ie, pituitary ACTH hypersecretion)	• Bilateral hyperplasia involving the zona fasciculata & reticularis
	Ectopic ACTH syndrome (eg, paraneoplastic ACTH secretion)	
ACTH-independent	Adrenal adenoma or carcinoma	• Benign tumors are typically round, well-circumscribed lesions with cells similar to normal zona fasciculata • Malignant tumors are often irregular and poorly demarcated with considerable cellular pleomorphism • Atrophy of the zona fasciculata & reticularis in the uninvolved cortex regions

This patient has symptoms of hypercortisolism, including weight gain, weakness, and easy bruising. She also has increased 24-hour urine excretion of cortisol and an elevated serum cortisol level that is not suppressed by low-dose dexamethasone, which confirm the diagnosis of Cushing syndrome. In addition, her ACTH level is elevated (ACTH-dependent Cushing syndrome), which is most commonly due to an ACTH-secreting corticotroph pituitary adenoma (**Cushing disease**).

Initially, **excess ACTH** rapidly acts to increase adrenal blood flow and metabolic activity, primarily within the zona fasciculata and reticularis. ACTH stimulates the transfer of cholesterol to the inner mitochondrial membrane by steroidogenic acute regulatory protein (the rate limiting step in steroid production) and its conversion to pregnenolone by cholesterol side-chain cleavage enzyme. Increased pregnenolone availability results in **increased cortisol synthesis** within the zona fasciculata and **increased androgen production** within the zona reticularis (can lead to irregular menstruation, hirsutism). ACTH also has a trophic (growth) effect on the **zona fasciculata and reticularis**; as time passes, high levels of ACTH upregulate RNA and protein synthesis and

https://t.me/USMLEWorldStep1

This patient has symptoms of hypercortisolism, including weight gain, weakness, and easy bruising. She also has increased 24-hour urine excretion of cortisol and an elevated serum cortisol level that is not suppressed by low-dose dexamethasone, which confirm the diagnosis of Cushing syndrome. In addition, her ACTH level is elevated (ACTH-dependent Cushing syndrome), which is most commonly due to an ACTH-secreting corticotroph pituitary adenoma (**Cushing disease**).

Initially, **excess ACTH** rapidly acts to increase adrenal blood flow and metabolic activity, primarily within the zona fasciculata and reticularis. ACTH stimulates the transfer of cholesterol to the inner mitochondrial membrane by steroidogenic acute regulatory protein (the rate limiting step in steroid production) and its conversion to pregnenolone by cholesterol side-chain cleavage enzyme. Increased pregnenolone availability results in **increased cortisol synthesis** within the zona fasciculata and **increased androgen production** within the zona reticularis (can lead to irregular menstruation, hirsutism). ACTH also has a trophic (growth) effect on the **zona fasciculata and reticularis**; as time passes, high levels of ACTH upregulate RNA and protein synthesis and induce cellular proliferation (**hyperplasia**).

(Choice A) Although increased ACTH can have a transient effect on aldosterone production, angiotensin II is the primary trophic hormone for the zona glomerulosa. Adenoma or nodular hyperplasia of the zona glomerulosa can be associated with increased secretion of mineralocorticoids (primary hyperaldosteronism [Conn syndrome]), which presents with hypertension and hypokalemia (muscle weakness).

(Choice B) Atrophy of the entire adrenal cortex is most commonly caused by autoimmune adrenalitis and presents with chronic adrenal insufficiency (Addison disease). There is a compensatory rise in ACTH secretion, but, unlike in this patient, urine cortisol excretion is not elevated.

(Choices C and E) Pheochromocytoma is a catecholamine-secreting tumor derived from the chromaffin cells of the adrenal medulla. Adrenal medullary hyperplasia is a rare disorder that may be a precursor to pheochromocytoma. These disorders typically present with symptoms of catecholamine excess (eg, palpitations, diaphoresis) and episodic hypertension. Patients have elevated blood and urine levels of catecholamines rather than cortisol.

Educational objective:
ACTH is the major trophic hormone of the zona fasciculata and reticularis, whereas the zona glomerulosa is

https://t.me/USMLEWorldStep1

(ACTH-dependent Cushing syndrome), which is most commonly due to an ACTH-secreting corticotroph pituitary adenoma (**Cushing disease**).

Initially, **excess ACTH** rapidly acts to increase adrenal blood flow and metabolic activity, primarily within the zona fasciculata and reticularis. ACTH stimulates the transfer of cholesterol to the inner mitochondrial membrane by steroidogenic acute regulatory protein (the rate limiting step in steroid production) and its conversion to pregnenolone by cholesterol side-chain cleavage enzyme. Increased pregnenolone availability results in **increased cortisol synthesis** within the zona fasciculata and **increased androgen production** within the zona reticularis (can lead to irregular menstruation, hirsutism). ACTH also has a trophic (growth) effect on the **zona fasciculata and reticularis**; as time passes, high levels of ACTH upregulate RNA and protein synthesis and induce cellular proliferation (**hyperplasia**).

(Choice A) Although increased ACTH can have a transient effect on aldosterone production, angiotensin II is the primary trophic hormone for the zona glomerulosa. Adenoma or nodular hyperplasia of the zona glomerulosa can be associated with increased secretion of mineralocorticoids (primary hyperaldosteronism [Conn syndrome]), which presents with hypertension and hypokalemia (muscle weakness).

(Choice B) Atrophy of the entire adrenal cortex is most commonly caused by autoimmune adrenalitis and presents with chronic adrenal insufficiency (Addison disease). There is a compensatory rise in ACTH secretion, but, unlike in this patient, urine cortisol excretion is not elevated.

(Choices C and E) Pheochromocytoma is a catecholamine-secreting tumor derived from the chromaffin cells of the adrenal medulla. Adrenal medullary hyperplasia is a rare disorder that may be a precursor to pheochromocytoma. These disorders typically present with symptoms of catecholamine excess (eg, palpitations, diaphoresis) and episodic hypertension. Patients have elevated blood and urine levels of catecholamines rather than cortisol.

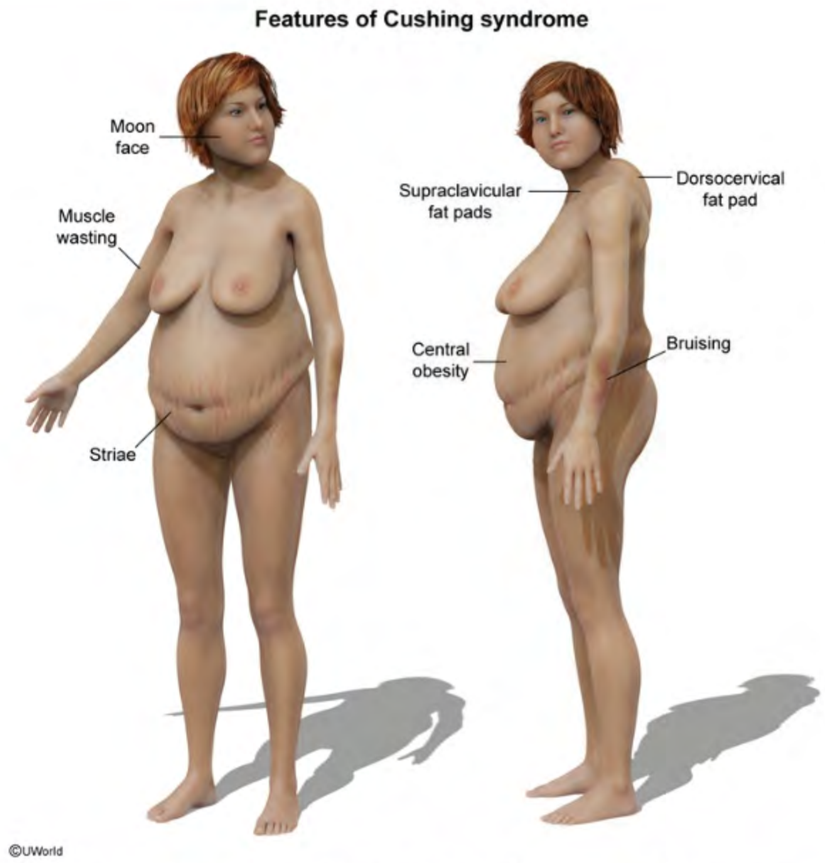
Educational objective:
ACTH is the major trophic hormone of the zona fasciculata and reticularis, whereas the zona glomerulosa is primarily regulated by angiotensin II. Excess production of ACTH causes increased cortisol synthesis within the zona fasciculata (Cushing's manifestations) and increased androgen production within the zona reticularis (irregular menstruation, hirsutism in women).

https://t.me/USMLEWorldStep1

zona fasciculata

Exhibit Display

Features of Cushing syndrome | Features of Cushing syndrome



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

This p
increa
dose c
(ACTH
adeno

Initially
fascicu
steroic
pregne
increa
reticul
fascic
induce

(Choic
primar
be ass
preser

(Choic
preser
but, u

(Choices C and E) Pheochromocytoma is a catecholamine-secreting tumor derived from the chromaffin cells of

https://t.me/USMLEWorldStep1

zona fasciculata

Exhibit Display

Features of Cushing syndrome | Features of Cushing syndrome

Features of Cushing syndrome	
Clinical manifestations	• **Central obesity** • Skin atrophy & wide, purplish **striae** • Proximal muscle weakness • Hypertension • **Glucose intolerance** • Skin hyperpigmentation (if due to ACTH excess) • Depression, anxiety
Diagnosis	• 24-hr urinary cortisol excretion • Late-night salivary cortisol assay • Low-dose dexamethasone suppression test

New | Existing | My Notebook

This p
increa
dose c
(ACTH
adeno

Initially
fascicu
steroic
pregne
increa
reticul
fascic
induce

(Choic
primar
be ass
preser

(Choic
preser
but, u

(Choices C and E) Pheochromocytoma is a catecholamine-secreting tumor derived from the chromaffin cells of

https://t.me/USMLEWorldStep1

A 58-year-old man is hospitalized due to sudden onset of chest pain. Blood pressure is 160/110 mm Hg and pulse is 90/min. BMI is 26.9 kg/m^2. A baseline ECG shows nonspecific ST-segment and T-wave abnormalities, and serial troponin measurements are normal. The patient's fasting plasma glucose level is 160 mg/dL, although he has not been diagnosed previously with diabetes mellitus. Serum triglyceride level is elevated, and the HDL level is low. Which of the following additional findings would be most suggestive of increased insulin resistance in this patient?

- A. Decreased hepatic glucose production
- B. Elevated LDL level
- C. High urine ketone concentration
- D. Increased glycogen stores in skeletal muscles
- E. Increased waist circumference

Submit

https://t.me/USMLEWorldStep1

A 58-year-old man is hospitalized due to sudden onset of chest pain. Blood pressure is 160/110 mm Hg and pulse is 90/min. BMI is 26.9 kg/m^2. A baseline ECG shows nonspecific ST-segment and T-wave abnormalities, and serial troponin measurements are normal. The patient's fasting plasma glucose level is 160 mg/dL, although he has not been diagnosed previously with diabetes mellitus. Serum triglyceride level is elevated, and the HDL level is low. Which of the following additional findings would be most suggestive of increased insulin resistance in this patient?

- A. Decreased hepatic glucose production (4%)
- ✗ B. Elevated LDL level (12%)
- C. High urine ketone concentration (17%)
- D. Increased glycogen stores in skeletal muscles (2%)
- ✓ E. Increased waist circumference (62%)

Incorrect
Correct answer
E

62%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

This patient has hypertension and likely **type 2 diabetes mellitus**. The primary defects in the pathophysiology of type 2 diabetes include **defective insulin secretion** from pancreatic beta cells and **insulin resistance** in peripheral tissues. Insulin resistance is caused by a number of genetic (eg, insulin receptor and postreceptor mutations) and environmental factors (eg, lack of physical activity, obesity).

An adipose body habitus is commonly associated with insulin resistance and type 2 diabetes. In particular, excess **visceral fat** (surrounding internal organs) correlates much more strongly with insulin resistance than does subcutaneous fat. Measurement of **waist circumference** or **waist-to-hip ratio** is an effective indirect assessment of visceral fat, especially in patients who are overweight (BMI 25-29.9 kg/m^2) or mildly obese (BMI 30-34.9 kg/m^2).

https://t.me/USMLEWorldStep1

This patient has hypertension and likely **type 2 diabetes mellitus**. The primary defects in the pathophysiology of type 2 diabetes include **defective insulin secretion** from pancreatic beta cells and **insulin resistance** in peripheral tissues. Insulin resistance is caused by a number of genetic (eg, insulin receptor and postreceptor mutations) and environmental factors (eg, lack of physical activity, obesity).

An adipose body habitus is commonly associated with insulin resistance and type 2 diabetes. In particular, excess **visceral fat** (surrounding internal organs) correlates much more strongly with insulin resistance than does subcutaneous fat. Measurement of **waist circumference** or **waist-to-hip ratio** is an effective indirect assessment of visceral fat, especially in patients who are overweight (BMI 25-29.9 kg/m^2) or mildly obese (BMI 30-34.9 kg/m^2). A waist circumference >102 cm (40 in) in men and >88 cm (35 in) in women is associated with a higher risk of insulin resistance.

The association of insulin resistance, increased visceral adiposity (ie, increased waist circumference), hypertension, and serum lipid abnormalities (high triglyceride levels, low HDL levels) is known as **metabolic syndrome** (sometimes called syndrome X). Patients with metabolic syndrome have increased rates of **cardiovascular events** and warrant careful risk factor management.

(Choice A) Insulin suppresses gluconeogenesis and promotes glycogen synthesis in the liver. In patients with insulin resistance, the inhibitory effect of insulin on gluconeogenesis is reduced, leading to increased hepatic glucose production.

(Choice B) High LDL levels are an independent risk factor for atherosclerotic heart disease in patients with diabetes, but are not directly associated with increased insulin resistance. In contrast, insulin resistance is associated with high triglyceride and low HDL levels.

(Choice C) High urinary excretion of ketones suggests absolute insulin deficiency, as seen in type 1 diabetes, rather than insulin resistance. Patients with type 2 diabetes and insulin resistance typically have high circulating insulin levels that are more than adequate to suppress ketone formation.

(Choice D) Skeletal muscle is a major repository for ingested glucose due to insulin-mediated glucose uptake. In patients with insulin resistance, decreased glucose uptake in skeletal muscle leads to reduced glycogen synthesis and higher blood glucose levels.

https://t.me/USMLEWorldStep1

mutations) and environmental factors (eg, lack of physical activity, obesity).

An adipose body habitus is commonly associated with insulin resistance and type 2 diabetes. In particular, excess **visceral fat** (surrounding internal organs) correlates much more strongly with insulin resistance than does subcutaneous fat. Measurement of **waist circumference** or **waist-to-hip ratio** is an effective indirect assessment of visceral fat, especially in patients who are overweight (BMI 25-29.9 kg/m^2) or mildly obese (BMI 30-34.9 kg/m^2). A waist circumference >102 cm (40 in) in men and >88 cm (35 in) in women is associated with a higher risk of insulin resistance.

The association of insulin resistance, increased visceral adiposity (ie, increased waist circumference), hypertension, and serum lipid abnormalities (high triglyceride levels, low HDL levels) is known as **metabolic syndrome** (sometimes called syndrome X). Patients with metabolic syndrome have increased rates of **cardiovascular events** and warrant careful risk factor management.

(Choice A) Insulin suppresses gluconeogenesis and promotes glycogen synthesis in the liver. In patients with insulin resistance, the inhibitory effect of insulin on gluconeogenesis is reduced, leading to increased hepatic glucose production.

(Choice B) High LDL levels are an independent risk factor for atherosclerotic heart disease in patients with diabetes, but are not directly associated with increased insulin resistance. In contrast, insulin resistance is associated with high triglyceride and low HDL levels.

(Choice C) High urinary excretion of ketones suggests absolute insulin deficiency, as seen in type 1 diabetes, rather than insulin resistance. Patients with type 2 diabetes and insulin resistance typically have high circulating insulin levels that are more than adequate to suppress ketone formation.

(Choice D) Skeletal muscle is a major repository for ingested glucose due to insulin-mediated glucose uptake. In patients with insulin resistance, decreased glucose uptake in skeletal muscle leads to reduced glycogen synthesis and higher blood glucose levels.

Educational objective:
Visceral obesity as measured by waist circumference or waist-to-hip ratio is an important predictor of insulin resistance.

https://t.me/USMLEWorldStep1

A 2-hour-old newborn has a blood glucose concentration of 30 mg/dL. The patient was delivered via caesarean to a 32-year-old woman at 38 weeks gestation. Birth weight is 4.5 kg (9 lb 14 oz). The pregnancy was complicated by gestational diabetes treated with insulin. However, glycemic control remained suboptimal due to maternal noncompliance with insulin treatment and poor adherence to dietary recommendations. Examination of the neonate is unremarkable. Which of the following is the most likely primary mechanism responsible for this patient's low blood glucose concentration?

- A. Decreased glycogen stores
- B. Hyperfunctioning pancreas
- C. Impaired hepatic glycogenolysis
- D. Increased release of cortisol
- E. Insulin resistance

Submit

https://t.me/USMLEWorldStep1

A 2-hour-old newborn has a blood glucose concentration of 30 mg/dL. The patient was delivered via caesarean to a 32-year-old woman at 38 weeks gestation. Birth weight is 4.5 kg (9 lb 14 oz). The pregnancy was complicated by gestational diabetes treated with insulin. However, glycemic control remained suboptimal due to maternal noncompliance with insulin treatment and poor adherence to dietary recommendations. Examination of the neonate is unremarkable. Which of the following is the most likely primary mechanism responsible for this patient's low blood glucose concentration?

- A. Decreased glycogen stores (4%)
- ✓ B. Hyperfunctioning pancreas (77%)
- C. Impaired hepatic glycogenolysis (7%)
- D. Increased release of cortisol (1%)
- E. Insulin resistance (8%)

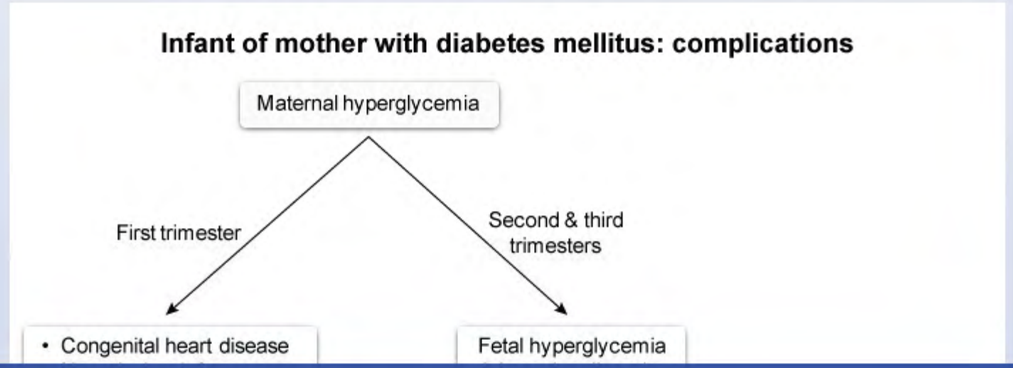
Correct

77% Answered correctly

03 secs Time Spent

2023 Version

Explanation

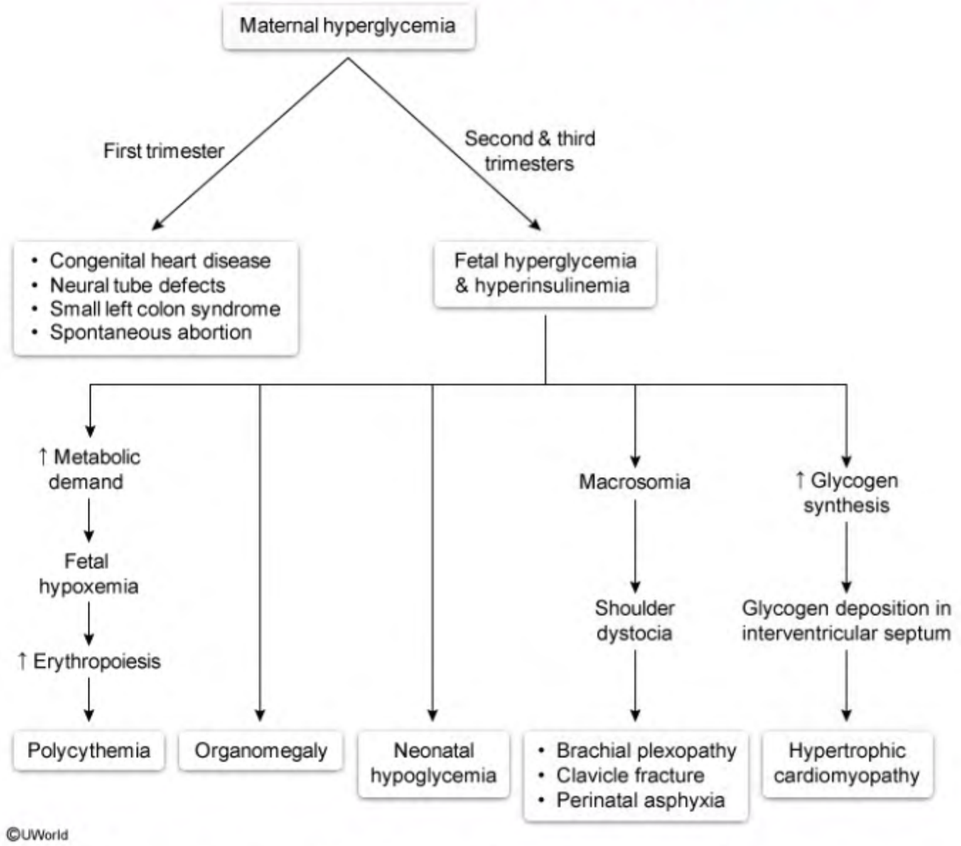


https://t.me/USMLEWorldStep1

A 2-hour-old newborn has a blood glucose concentration of 30 mg/dL. The patient was delivered via caesarean to a 32-y
by ges
nonco
neona
low bl

Exhibit Display

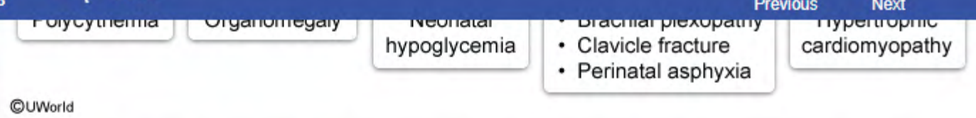
Infant of mother with diabetes mellitus: complications



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

• Congenital heart disease
Fetal hyperglycemia

https://t.me/USMLEWorldStep1



©UWorld

Glucose levels fall in all newborns after birth, but usually remain ≥40 mg/dL due to mobilization of hepatic glycogen stores and initiation of feeding; glucose <40 mg/dL is indicative of **neonatal hypoglycemia**, a common metabolic derangement seen in **infants of diabetic mothers**.

During gestation, glucose is transferred continuously from mother to fetus via the placenta. Mothers with diabetes, particularly those with poor glycemic control, often have hyperglycemia, causing **fetal hyperglycemia**. In utero, this results in compensatory **hyperfunctioning of pancreatic beta cells**, which then produce increased amounts of insulin to handle the excessive glucose load. Once the maternal glucose supply is interrupted at delivery, persistent **hyperinsulinemia** causes increased glucose consumption and transient neonatal hypoglycemia.

Most neonates with hypoglycemia are asymptomatic but may develop autonomic symptoms (eg, jitteriness, irritability) and, if severe, hypotonia and seizures. **Macrosomia** (>4 kg [8 lb 14 oz] birth weight) is also common in infants of diabetic mothers due to increased exposure to growth factors (eg, insulin, insulin-like growth factors, growth hormone) that stimulate fetal growth and increased deposition of glycogen and fat in developing tissues **(Choice A)**.

(Choice C) Hypoglycemia due to impaired hepatic glycogenolysis is characteristic of certain glycogen storage diseases (eg, von Gierke disease, Cori disease), which typically present within the first several months of life with failure to thrive, ketotic hypoglycemia, and hepatomegaly (ie, protruding abdomen) due to increased hepatic glycogen content.

(Choices D and E) Critically ill infants may produce increased cortisol due to stress (eg, sepsis, mechanical ventilation) with resultant hyperglycemia. Insulin resistance, which is not typically seen in infants but is related to obesity in children and adults, also causes hyperglycemia. However, this neonate is hypoglycemic.

Educational objective:
Neonatal hypoglycemia is common in infants of diabetic mothers. The pathophysiology involves maternal hyperglycemia, which in turn causes fetal hyperglycemia and compensatory hyperfunctioning of the pancreas (ie, hyperinsulinemia). After birth, persistently elevated insulin levels lead to transient hypoglycemia.

https://t.me/USMLEWorldStep1

A 60-year-old man comes to the office for follow-up of type 2 diabetes mellitus. His treatment regimen includes oral medications and a once-daily injection of long-acting subcutaneous insulin. The patient is adherent with treatment and has modified his lifestyle. Review of home glucose measurements shows that his postprandial glucose levels are frequently elevated; however, fasting levels are normal. He has no other medical conditions and does not use tobacco, alcohol, or recreational drugs. Vital signs are within normal limits. Physical examination shows no abnormalities. Hemoglobin A1c is 8.3%. Additional insulin therapy 3 times a day before each meal is planned to improve glycemic control. Which of the following types of insulin is most appropriate for this patient?

- A. Insulin aspart
- B. Insulin degludec
- C. Insulin detemir
- D. Insulin glargine
- E. NPH insulin

Submit

https://t.me/USMLEWorldStep1

A 60-year-old man comes to the office for follow-up of type 2 diabetes mellitus. His treatment regimen includes oral medications and a once-daily injection of long-acting subcutaneous insulin. The patient is adherent with treatment and has modified his lifestyle. Review of home glucose measurements shows that his postprandial glucose levels are frequently elevated; however, fasting levels are normal. He has no other medical conditions and does not use tobacco, alcohol, or recreational drugs. Vital signs are within normal limits. Physical examination shows no abnormalities. Hemoglobin A1c is 8.3%. Additional insulin therapy 3 times a day before each meal is planned to improve glycemic control. Which of the following types of insulin is most appropriate for this patient?

- ✓ A. Insulin aspart (75%)
- ✗ B. Insulin degludec (2%)
- C. Insulin detemir (3%)
- D. Insulin glargine (9%)
- E. NPH insulin (9%)

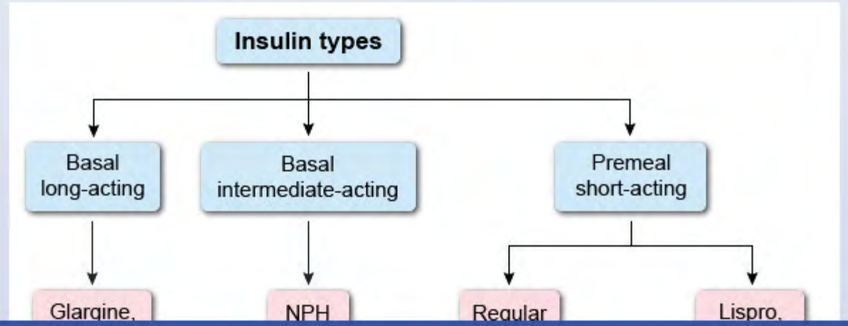
Incorrect
Correct answer
A

75%
Answered correctly

03 secs
Time Spent

2023
Version

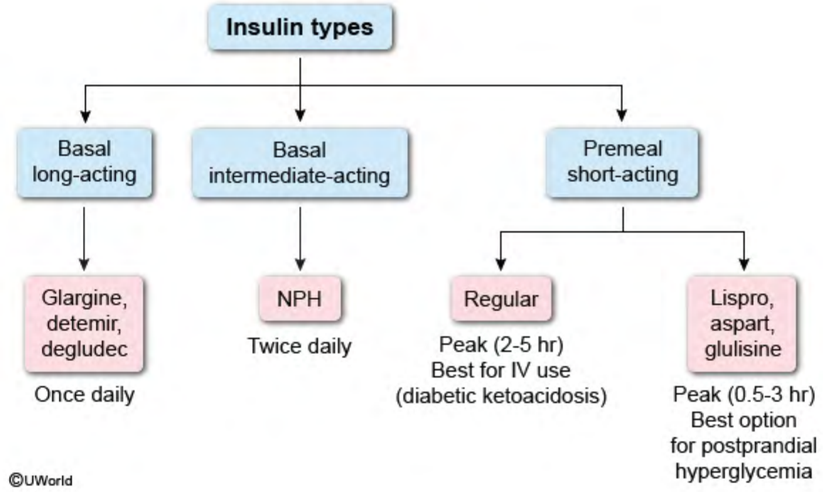
Explanation



https://t.me/USMLEWorldStep1

A 60-year-old man comes to the office for follow-up of type 2 diabetes mellitus. His treatment regimen includes oral m
treatm
glucos
does r
shows
planne

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1



The beta cells of the pancreas produce **basal insulin** continuously at a low level to suppress on-going hepatic gluconeogenesis. After meals, insulin secretion increases briefly to control the **postprandial** rise in blood glucose. Commercial insulin analogues with different pharmacokinetics can be given subcutaneously to replicate physiologic insulin secretion:

- **Long-acting insulins** (eg, glargine) mimic basal insulin secretion; they have an extended duration of action and little or no peak effect. They are typically given once daily and suppress **fasting hyperglycemia,** which is predominantly caused by inappropriate hepatic gluconeogenesis.
- **Rapid-acting insulins** (eg, lispro, aspart) are given to mimic the effects of postprandial insulin; they **peak quickly** and are then rapidly cleared. They are given prior to meals so that the peak effect coincides with postmeal glucose excursions; they control **postprandial hyperglycemia**. Because they are quickly cleared, they have minimal effect on fasting glucose levels.

This patient has normal fasting glucose levels, suggesting that his long-acting basal insulin regimen is appropriate but that he has elevated postprandial glucose. His postprandial hyperglycemia is best treated with a **rapid-acting premeal insulin analogue**, such as **aspart**, lispro, or glulisine. Regular insulin also can be given before mealtimes but has a more delayed peak onset and a longer duration of action compared to rapid-acting insulin analogues (which have amino acid changes that accelerate hexamer dissociation compared to regular insulin).

(Choices B, C, and D) Insulins degludec, detemir, and glargine have long durations of action due to structural modifications (eg, polymerizing residues, fatty acid side chains) that delay absorption and distribution. They have minimal peak effect and are used as basal insulin substitutes.

(Choice E) NPH, an intermediate-acting crystalline suspension of insulin with zinc/protamine, can be given twice daily when used as basal insulin. However, unlike other basal insulins, it has a noticeable peak effect and can lead to hypoglycemia if the peak does not correspond to a meal (eg, nocturnal hypoglycemia), making it a less preferable option for this use.

https://t.me/USMLEWorldStep1

gluconeogenesis. After meals, insulin secretion increases briefly to control the **postprandial** rise in blood glucose. Commercial insulin analogues with different pharmacokinetics can be given subcutaneously to replicate physiologic insulin secretion:

- **Long-acting insulins** (eg, glargine) mimic basal insulin secretion; they have an extended duration of action and little or no peak effect. They are typically given once daily and suppress **fasting hyperglycemia,** which is predominantly caused by inappropriate hepatic gluconeogenesis.
- **Rapid-acting insulins** (eg, lispro, aspart) are given to mimic the effects of postprandial insulin; they **peak quickly** and are then rapidly cleared. They are given prior to meals so that the peak effect coincides with postmeal glucose excursions; they control **postprandial hyperglycemia**. Because they are quickly cleared, they have minimal effect on fasting glucose levels.

This patient has normal fasting glucose levels, suggesting that his long-acting basal insulin regimen is appropriate but that he has elevated postprandial glucose. His postprandial hyperglycemia is best treated with a **rapid-acting premeal insulin analogue**, such as **aspart**, lispro, or glulisine. Regular insulin also can be given before mealtimes but has a more delayed peak onset and a longer duration of action compared to rapid-acting insulin analogues (which have amino acid changes that accelerate hexamer dissociation compared to regular insulin).

(Choices B, C, and D) Insulins degludec, detemir, and glargine have long durations of action due to structural modifications (eg, polymerizing residues, fatty acid side chains) that delay absorption and distribution. They have minimal peak effect and are used as basal insulin substitutes.

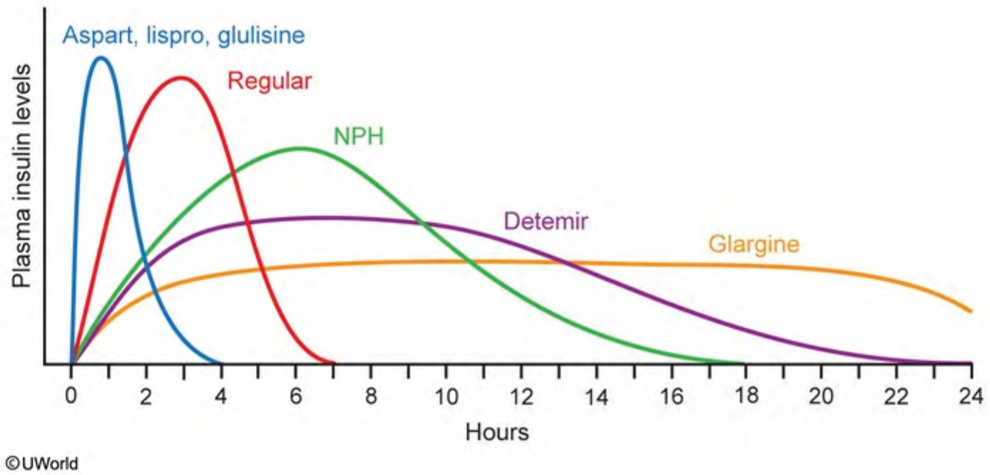
(Choice E) NPH, an intermediate-acting crystalline suspension of insulin with zinc/protamine, can be given twice daily when used as basal insulin. However, unlike other basal insulins, it has a noticeable peak effect and can lead to hypoglycemia if the peak does not correspond to a meal (eg, nocturnal hypoglycemia), making it a less preferable option for this use.

Educational objective:
Long-acting insulin analogues (eg, glargine) have an extended duration of action without a noticeable peak in activity and are typically given once daily to mimic basal insulin secretion. Rapid-acting insulins (eg, aspart, lispro) are quickly absorbed from the injection site and are given at mealtimes to replicate postprandial insulin secretion.

https://t.me/USMLEWorldStep1

- **Long-acting insulins** (eg, glargine) mimic basal insulin secretion; they have an extended duration of action

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

This p
but tha
preme
mealti
analog

(Choi
modifi
minim

(Choi
daily w
to hyp
prefer

Educa
Long-a
activity
are qu

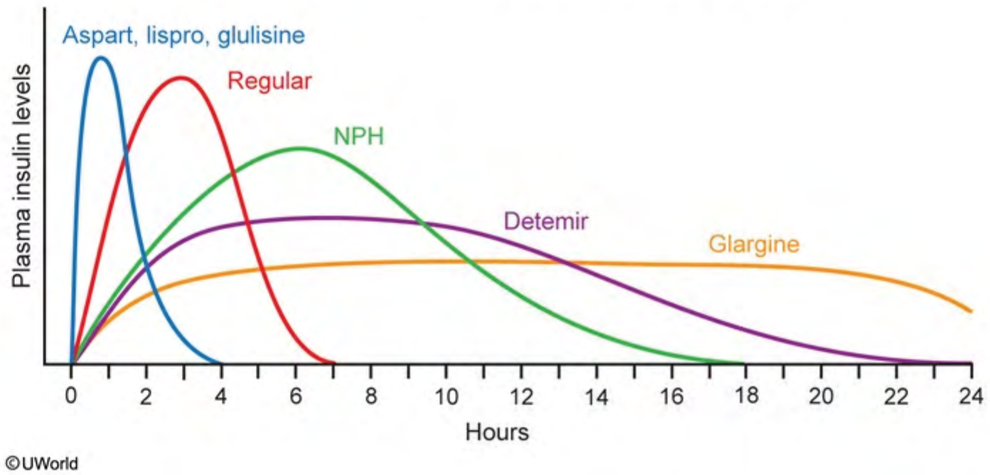
Pharma
Subject

Copyright © UWorld. All rights reserved.

https://t.me/USMLEWorldStep1

- **Long-acting insulins** (eg, glargine) mimic basal insulin secretion; they have an extended duration of action

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

This p
but tha
preme
mealti
analog

(Choi
modifi
minim

(Choi
daily w
to hyp
prefer

Educa
Long-a
activity
are qu

Pharma
Subject

Copyright © UWorld. All rights reserved.

https://t.me/USMLEWorldStep1

A 1-hour-old boy in the newborn nursery is evaluated for jitteriness and irritability. The neonate was born by cesarean delivery due to arrest of the second stage of labor. The patient has not yet breastfed as his mother is still recovering from surgery. The mother's pregnancy was complicated by gestational diabetes mellitus; she was prescribed insulin but did not take it regularly. Birth weight is 4.5 kg (9 lb 15 oz). Cardiopulmonary examination is within normal limits. Serum glucose is 21 mg/dL. Which of the following is the most likely cause of this neonate's hypoglycemia?

- A. Decreased fetal hepatic glycogen concentration
- B. Fetal pancreatic beta cell hyperplasia
- C. Increased fetal insulin-like growth factor 2 production
- D. Increased fetal pituitary gland growth hormone release
- E. Placental transfer of insulin to the fetus

Submit

https://t.me/USMLEWorldStep1

A 1-hour-old boy in the newborn nursery is evaluated for jitteriness and irritability. The neonate was born by cesarean delivery due to arrest of the second stage of labor. The patient has not yet breastfed as his mother is still recovering from surgery. The mother's pregnancy was complicated by gestational diabetes mellitus; she was prescribed insulin but did not take it regularly. Birth weight is 4.5 kg (9 lb 15 oz). Cardiopulmonary examination is within normal limits. Serum glucose is 21 mg/dL. Which of the following is the most likely cause of this neonate's hypoglycemia?

- A. Decreased fetal hepatic glycogen concentration (7%)
- ✓ B. Fetal pancreatic beta cell hyperplasia (74%)
- C. Increased fetal insulin-like growth factor 2 production (7%)
- D. Increased fetal pituitary gland growth hormone release (1%)
- E. Placental transfer of insulin to the fetus (9%)

Correct

74% Answered correctly

03 secs Time Spent

2023 Version

Explanation

Neonatal complications of diabetes during pregnancy	
Pathogenesis	• Maternal hyperglycemia → fetal hyperglycemia → β-cell hyperplasia & hyperinsulinemia
Associated risks	• Hypoglycemia after delivery • Prematurity/respiratory distress syndrome • Congenital anomalies (eg, caudal regression syndrome)

https://t.me/USMLEWorldStep1

Neonatal complications of diabetes during pregnancy	
Pathogenesis	• Maternal hyperglycemia → fetal hyperglycemia → β-cell hyperplasia & hyperinsulinemia
Associated risks	• Hypoglycemia after delivery • Prematurity/respiratory distress syndrome • Congenital anomalies (eg, caudal regression syndrome) • Macrosomia (brachial plexus injury, clavicle fracture) • Polycythemia (↑ metabolic requirements)

During pregnancy, human placental lactogen is secreted from the placenta in increasing quantities in the second and third trimesters, resulting in maternal insulin resistance. This physiologic process in pregnancy helps to supply the developing fetus with a reliable source of glucose. However, it becomes pathologic when maternal pancreatic function is not sufficient to overcome the pregnancy-related increase in insulin resistance, resulting in **gestational diabetes mellitus**.

Elevated maternal blood glucose leads to excessive transplacental transfer of glucose to the fetus, causing chronic stimulation of the **fetal pancreas**. This results in **beta cell hyperplasia** and hyperinsulinism. High levels of both fetal insulin (an anabolic hormone) and glucose promote development of fetal macrosomia with increased central adipose deposition.

After delivery, the infant experiences a sudden interruption in transplacental glucose transfer, but the hyperinsulinism remains due to beta cell hyperplasia. This can result in rapid development of profound transient **hypoglycemia**. In most cases, supportive care only is needed as the beta cell hyperplasia will resolve over time.

(Choice A) Insulin promotes blood glucose storage in the liver as glycogen; therefore, infants of mothers with poorly controlled diabetes have increased glycogen stores. However, after birth these infants have poor mobilization of glycogen stores (glycogenolysis) despite hypoglycemia due to high levels of insulin from islet hyperplasia.

https://t.me/USMLEWorldStep1

Elevated maternal blood glucose leads to excessive transplacental transfer of glucose to the fetus, causing chronic stimulation of the **fetal pancreas**. This results in **beta cell hyperplasia** and hyperinsulinism. High levels of both fetal insulin (an anabolic hormone) and glucose promote development of fetal macrosomia with increased central adipose deposition.

After delivery, the infant experiences a sudden interruption in transplacental glucose transfer, but the hyperinsulinism remains due to beta cell hyperplasia. This can result in rapid development of profound transient **hypoglycemia**. In most cases, supportive care only is needed as the beta cell hyperplasia will resolve over time.

(Choice A) Insulin promotes blood glucose storage in the liver as glycogen; therefore, infants of mothers with poorly controlled diabetes have increased glycogen stores. However, after birth these infants have poor mobilization of glycogen stores (glycogenolysis) despite hypoglycemia due to high levels of insulin from islet hyperplasia.

(Choice C) Fetal hyperglycemia may result in increased secretion of insulin-like growth factor 2 (IGF-2) during gestation, contributing to fetal macrosomia; however, neonatal hypoglycemia is primarily caused by hyperinsulinemia that persists after birth.

(Choice D) Growth hormone is released from the anterior pituitary gland and causes increased insulin resistance, decreasing peripheral uptake of glucose and elevating circulating glucose levels. Therefore, an increase in fetal growth hormone release would result in hyperglycemia.

(Choice E) Maternal insulin is not transferred to the fetus but instead is catabolized by the placenta. It is the fetal pancreatic production of insulin that leads to transient neonatal hypoglycemia.

Educational objective:
Maternal hyperglycemia causes increased transplacental transfer of glucose to the infant, resulting in fetal hyperglycemia and subsequent pancreatic beta cell hyperplasia. The pancreatic beta cell hyperplasia causes hyperinsulinemia, leading to fetal macrosomia and neonatal hypoglycemia.

Pathophysiology	Endocrine, Diabetes & Metabolism	Gestational diabetes
Subject	System	Topic

https://t.me/USMLEWorldStep1

A 4-day-old infant is brought to the emergency department due to abnormal movements. The patient has had intermittent episodes of tonic posturing over the past 3 hours as well as vomiting, poor feeding, and irritability for the past 2 days. The mother also reports that the infant's diapers smell like caramelizing sugar. There are no known medical conditions in the family, but the mother's sister died "sometime in the first year" of life from unknown causes. On examination, the patient is lethargic and demonstrates intermittent posturing and increased generalized muscle tone. Laboratory evaluation of plasma and urine samples confirms the suspected diagnosis. This patient is most likely deficient in an enzyme that requires which of the following substances?

- A. Arginine
- B. Cobalamin
- C. Pyridoxine
- D. Tetrahydrobiopterin
- E. Thiamine

Submit

https://t.me/USMLEWorldStep1

A 4-day-old infant is brought to the emergency department due to abnormal movements. The patient has had intermittent episodes of tonic posturing over the past 3 hours as well as vomiting, poor feeding, and irritability for the past 2 days. The mother also reports that the infant's diapers smell like caramelizing sugar. There are no known medical conditions in the family, but the mother's sister died "sometime in the first year" of life from unknown causes. On examination, the patient is lethargic and demonstrates intermittent posturing and increased generalized muscle tone. Laboratory evaluation of plasma and urine samples confirms the suspected diagnosis. This patient is most likely deficient in an enzyme that requires which of the following substances?

- ✗ A. Arginine (11%)
- B. Cobalamin (5%)
- C. Pyridoxine (22%)
- D. Tetrahydrobiopterin (17%)
- ✓ E. Thiamine (42%)

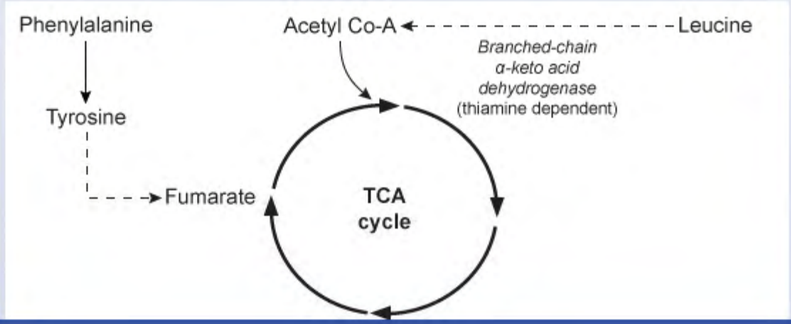
Incorrect
Correct answer
E

42%
Answered correctly

04 secs
Time Spent

2023
Version

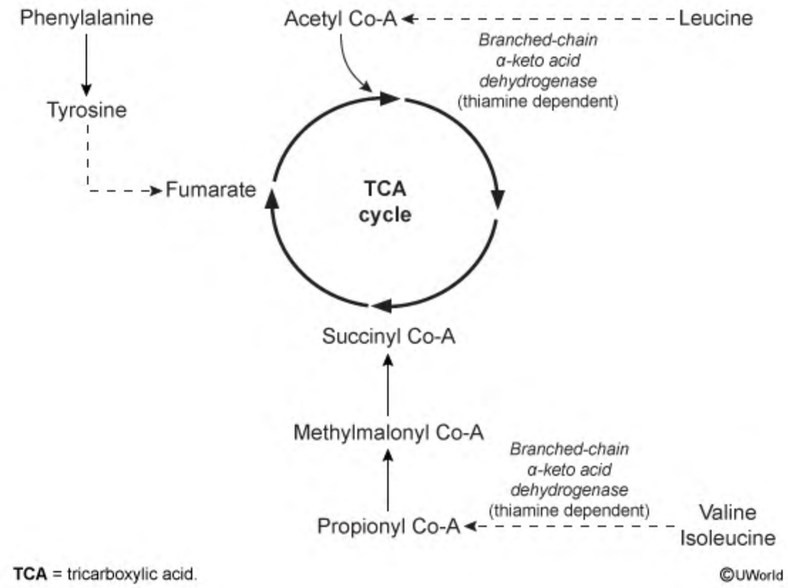
Explanation



https://t.me/USMLEWorldStep1

B. Cobalamin (5%)

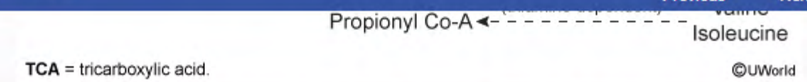
Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

This in
MSUD
enzyme necessary for breaking down the branched-chain amino acids (BCAAs) **leucine**, **isoleucine**, and **valine**.

https://t.me/USMLEWorldStep1



TCA = tricarboxylic acid.

©UWorld

This infant has symptoms typical of **maple syrup urine disease** (MSUD), an autosomal recessive disorder. MSUD is characterized by mutations in **branched-chain alpha-keto acid** dehydrogenase complex (BCKDC), an enzyme necessary for breaking down the branched-chain amino acids (BCAAs) **leucine**, **isoleucine**, and **valine**.

Defective BCKDC leads to accumulation of BCAAs in serum and peripheral tissues, resulting in **neurotoxicity** (eg, seizures, irritability, lethargy, and poor feeding) that can be life-threatening if untreated. A metabolite of isoleucine also gives the urine a **distinctive odor** described as **sweet**.

Treatment for MSUD involves restricting BCAAs in the diet. BCKDC (in addition to pyruvate dehydrogenase and alpha-ketoglutarate dehydrogenase) requires 5 cofactors: **thiamine**, lipoate, and coenzymes A, FAD, and NAD. Because MSUD has a spectrum of phenotypes, patients who have only a mild reduction in BCKDC activity may improve with high-dose thiamine treatment; however, most patients still require lifelong dietary restriction.

(Choice A) Treatment of most urea cycle disorders involves supplemental arginine. Arginine administration increases production of downstream water-soluble intermediate metabolites (eg, ornithine, citrulline), facilitating nitrogen disposal and decreasing plasma ammonia levels.

(Choice B) Cobalamin (vitamin B_{12}) deficiency leads to megaloblastic anemia, neurologic changes including peripheral neuropathy, and elevated plasma levels of homocysteine (a prothrombotic substance). Supplementation of cobalamin is recommended to lower homocysteine levels in patients with hyperhomocysteinemia.

(Choice C) Pyridoxine (vitamin B_6) is involved in the transamination and decarboxylation steps in amino acid metabolism as well as heme and neurotransmitter synthesis. Supplemental pyridoxine is typically prescribed in conjunction with drugs known to interfere with vitamin B_6 metabolism (eg, isoniazid, penicillamine).

(Choice D) Tetrahydrobiopterin deficiency results in phenylketonuria because tetrahydrobiopterin is a cofactor for phenylalanine hydroxylase. Phenylalanine levels can be reduced by tetrahydrobiopterin supplementation in patients with tetrahydrobiopterin deficiency.

Educational objective:
Maple syrup urine disease (MSUD) is caused by a deficiency of branched-chain alpha-keto acid dehydrogenase,

https://t.me/USMLEWorldStep1

MSUD is characterized by mutations in **branched-chain alpha-keto acid** dehydrogenase complex (BCKDC), an enzyme necessary for breaking down the branched-chain amino acids (BCAAs) **leucine**, **isoleucine**, and **valine**.

Defective BCKDC leads to accumulation of BCAAs in serum and peripheral tissues, resulting in **neurotoxicity** (eg, seizures, irritability, lethargy, and poor feeding) that can be life-threatening if untreated. A metabolite of isoleucine also gives the urine a **distinctive odor** described as **sweet**.

Treatment for MSUD involves restricting BCAAs in the diet. BCKDC (in addition to pyruvate dehydrogenase and alpha-ketoglutarate dehydrogenase) requires 5 cofactors: **thiamine**, lipoate, and coenzymes A, FAD, and NAD. Because MSUD has a spectrum of phenotypes, patients who have only a mild reduction in BCKDC activity may improve with high-dose thiamine treatment; however, most patients still require lifelong dietary restriction.

(Choice A) Treatment of most urea cycle disorders involves supplemental arginine. Arginine administration increases production of downstream water-soluble intermediate metabolites (eg, ornithine, citrulline), facilitating nitrogen disposal and decreasing plasma ammonia levels.

(Choice B) Cobalamin (vitamin B_{12}) deficiency leads to megaloblastic anemia, neurologic changes including peripheral neuropathy, and elevated plasma levels of homocysteine (a prothrombotic substance). Supplementation of cobalamin is recommended to lower homocysteine levels in patients with hyperhomocysteinemia.

(Choice C) Pyridoxine (vitamin B_6) is involved in the transamination and decarboxylation steps in amino acid metabolism as well as heme and neurotransmitter synthesis. Supplemental pyridoxine is typically prescribed in conjunction with drugs known to interfere with vitamin B_6 metabolism (eg, isoniazid, penicillamine).

(Choice D) Tetrahydrobiopterin deficiency results in phenylketonuria because tetrahydrobiopterin is a cofactor for phenylalanine hydroxylase. Phenylalanine levels can be reduced by tetrahydrobiopterin supplementation in patients with tetrahydrobiopterin deficiency.

Educational objective:
Maple syrup urine disease (MSUD) is caused by a deficiency of branched-chain alpha-keto acid dehydrogenase, an enzyme that requires several coenzymes (thiamine; lipoate; coenzymes A, FAD, NAD) to metabolize branched-chain amino acids (BCAAs). Some patients with milder forms of MSUD improve with high-dose thiamine treatment.

https://t.me/USMLEWorldStep1

seizures, irritability, lethargy, and poor feeding) that can be life-threatening if untreated. A metabolite of isoleucine also gives the urine a **distinctive odor** described as **sweet**.

Treatment for MSUD involves restricting BCAAs in the diet. BCKDC (in addition to pyruvate dehydrogenase and alpha-ketoglutarate dehydrogenase) requires 5 cofactors: **thiamine**, lipoate, and coenzymes A, FAD, and NAD. Because MSUD has a spectrum of phenotypes, patients who have only a mild reduction in BCKDC activity may improve with high-dose thiamine treatment; however, most patients still require lifelong dietary restriction.

(Choice A) Treatment of most urea cycle disorders involves supplemental arginine. Arginine administration increases production of downstream water-soluble intermediate metabolites (eg, ornithine, citrulline), facilitating nitrogen disposal and decreasing plasma ammonia levels.

(Choice B) Cobalamin (vitamin B_{12}) deficiency leads to megaloblastic anemia, neurologic changes including peripheral neuropathy, and elevated plasma levels of homocysteine (a prothrombotic substance). Supplementation of cobalamin is recommended to lower homocysteine levels in patients with hyperhomocysteinemia.

(Choice C) Pyridoxine (vitamin B_6) is involved in the transamination and decarboxylation steps in amino acid metabolism as well as heme and neurotransmitter synthesis. Supplemental pyridoxine is typically prescribed in conjunction with drugs known to interfere with vitamin B_6 metabolism (eg, isoniazid, penicillamine).

(Choice D) Tetrahydrobiopterin deficiency results in phenylketonuria because tetrahydrobiopterin is a cofactor for phenylalanine hydroxylase. Phenylalanine levels can be reduced by tetrahydrobiopterin supplementation in patients with tetrahydrobiopterin deficiency.

Educational objective:
Maple syrup urine disease (MSUD) is caused by a deficiency of branched-chain alpha-keto acid dehydrogenase, an enzyme that requires several coenzymes (thiamine; lipoate; coenzymes A, FAD, NAD) to metabolize branched-chain amino acids (BCAAs). Some patients with milder forms of MSUD improve with high-dose thiamine treatment.

References

- Branched-chain amino acid metabolism: from rare Mendelian diseases to more common disorders.
- Maple syrup urine disease.

https://t.me/USMLEWorldStep1

MSUD is characterized by mutations in **branched-chain alpha-keto acid** dehydrogenase complex (BCKDC), an enzyme necessary for breaking down the branched-chain amino acids (BCAAs) **leucine**, **isoleucine**, and **valine**.

Defect
seizur
also gi

Treatn
alpha-
Becau
improv

(Choi
increa
nitroge

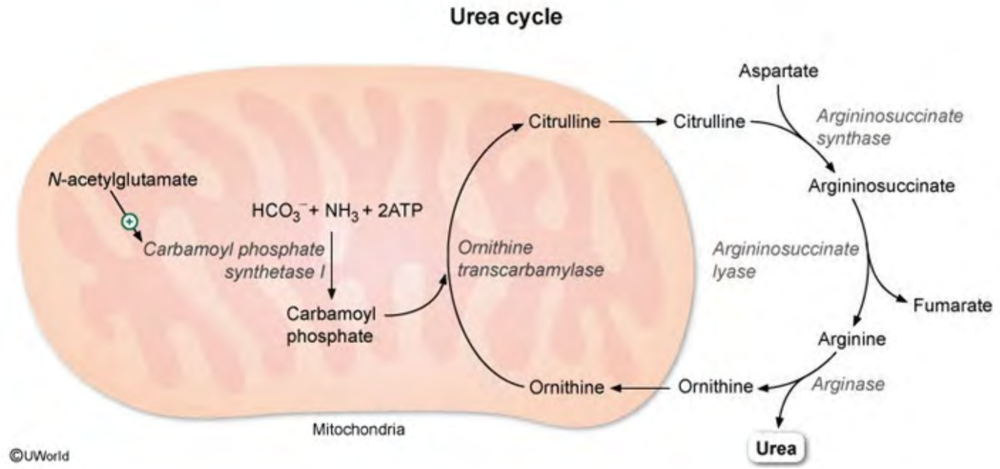
(Choi
periph
of cob

(Choi
metab
conjur

(Choi
pheny
patien

Educa
Maple
an enz
chain
treatment.

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

A 65-year-old man with benign prostatic hyperplasia comes to the office for a follow-up appointment. He has a history of obstructive urinary symptoms that were unrelieved with tamsulosin, and a new medication was prescribed at his last visit 8 months ago. Since starting the new medication, the patient has experienced gradual improvement in urinary hesitancy and strength of urinary stream. However, he also has noticed a significant increase in the size of his breasts. The patient reports no pain or changes in weight. Glandular tissue, approximately 2 cm in diameter, is palpated under the nipples and is mildly tender to palpation. There is no nipple discharge, breast asymmetry, or rash. This patient's breast findings are most likely due to which of the following drug effects?

- A. Blockade of androgen receptors
- B. Decreased testicular production of testosterone
- C. Displacement of estrogen from sex hormone–binding globulin
- D. Increased peripheral conversion of testosterone to estradiol
- E. Increased prolactin production

Submit

https://t.me/USMLEWorldStep1

A 65-year-old man with benign prostatic hyperplasia comes to the office for a follow-up appointment. He has a history of obstructive urinary symptoms that were unrelieved with tamsulosin, and a new medication was prescribed at his last visit 8 months ago. Since starting the new medication, the patient has experienced gradual improvement in urinary hesitancy and strength of urinary stream. However, he also has noticed a significant increase in the size of his breasts. The patient reports no pain or changes in weight. Glandular tissue, approximately 2 cm in diameter, is palpated under the nipples and is mildly tender to palpation. There is no nipple discharge, breast asymmetry, or rash. This patient's breast findings are most likely due to which of the following drug effects?

- ✗ A. Blockade of androgen receptors (21%)
- B. Decreased testicular production of testosterone (8%)
- C. Displacement of estrogen from sex hormone–binding globulin (3%)
- ✓ D. Increased peripheral conversion of testosterone to estradiol (63%)
- E. Increased prolactin production (3%)

Incorrect
Correct answer
D

63%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

Medication-induced gynecomastia*	
Drug	**Mechanism**
Estrogens	Direct stimulation of ductal epithelial hyperplasia
Antiandrogens (eg, flutamide, bicalutamide)	Competitive inhibition of testosterone receptor

https://t.me/USMLEWorldStep1

Explanation

Medication-induced gynecomastia*	
Drug	**Mechanism**
Estrogens	Direct stimulation of ductal epithelial hyperplasia
Antiandrogens (eg, flutamide, bicalutamide)	Competitive inhibition of testosterone receptor
5-alpha reductase inhibitors (eg, finasteride)	↓ Conversion of testosterone to dihydrotestosterone
Spironolactone	↓ Testosterone synthesis & inhibition of testosterone receptor
Ketoconazole	↓ Synthesis of steroid hormones (↓ androgen > ↓ estrogen)
Cimetidine	Inhibition of testosterone receptor
Androgen-anabolic steroids	Aromatization of androgens to estrogen
*Drugs that increase the estrogen/testosterone ratio are associated with gynecomastia.	

Gynecomastia is the abnormal development of glandular breast tissue in males. It is characterized by ductal epithelial hyperplasia with fibrosis of the surrounding stroma. Breast growth is inhibited by androgens and promoted by estrogens; conditions that cause **increased estrogen/androgen ratio** can lead to gynecomastia.

This patient, who did not respond to first-line therapy (ie, tamsulosin, an alpha-adrenergic antagonist) for benign prostatic hyperplasia, has likely been prescribed a **5-alpha reductase inhibitor** (eg, finasteride, dutasteride). These medications **block conversion of testosterone to dihydrotestosterone**, which has a higher affinity for the testosterone receptor and mediates most testosterone effects (including prostatic hyperplasia).

However, the **excess testosterone** is then **converted to estrogen** (eg, estradiol) by aromatase in various tissues (eg, adipose, bone), leading to gynecomastia. Both the beneficial effects and potential gynecomastia of 5-alpha

https://t.me/USMLEWorldStep1

Gynecomastia is the abnormal development of glandular breast tissue in males. It is characterized by ductal epithelial hyperplasia with fibrosis of the surrounding stroma. Breast growth is inhibited by androgens and promoted by estrogens; conditions that cause **increased estrogen/androgen ratio** can lead to gynecomastia.

This patient, who did not respond to first-line therapy (ie, tamsulosin, an alpha-adrenergic antagonist) for benign prostatic hyperplasia, has likely been prescribed a **5-alpha reductase inhibitor** (eg, finasteride, dutasteride). These medications **block conversion of testosterone to dihydrotestosterone**, which has a higher affinity for the testosterone receptor and mediates most testosterone effects (including prostatic hyperplasia).

However, the **excess testosterone** is then **converted to estrogen** (eg, estradiol) by aromatase in various tissues (eg, adipose, bone), leading to gynecomastia. Both the beneficial effects and potential gynecomastia of 5-alpha reductase inhibitors develop slowly and are generally not apparent in the first several months of therapy.

(Choice A) Androgen receptor antagonists (eg, flutamide, bicalutamide) are competitive inhibitors that block the binding of androgens in target tissues; these agents are widely used in metastatic prostate cancer but not for treating BPH.

(Choices B and C) Ketoconazole is an antifungal agent that inhibits enzymes in the steroid hormone biosynthetic pathway, reducing testosterone synthesis. Spironolactone is an aldosterone receptor antagonist that also decreases testosterone synthesis in addition to cross-inhibition of the androgen receptor. Both drugs also can displace estrogen from plasma binding proteins and raise free estrogen levels, but neither is used in BPH.

(Choice E) Pituitary prolactin secretion is under negative regulation by dopamine. Dopamine receptor antagonists (eg, antipsychotic medications) facilitate increased prolactin release and can occasionally cause galactorrhea. The resulting hyperprolactinemia can also suppress release of FSH and LH, leading to central hypogonadism (and rarely gynecomastia).

Educational objective:
5-alpha reductase inhibitors (eg, finasteride, dutasteride) are used in the treatment of benign prostatic hyperplasia. They block the conversion of testosterone to dihydrotestosterone; the excess testosterone is then available for conversion to estrogens (eg, estradiol) by aromatase, which can lead to gynecomastia.

References

https://t.me/USMLEWorldStep1

Gynecomastia is the abnormal development of glandular breast tissue in males. It is characterized by ductal epithe
promo

This p
prosta
These
testos

Howev
(eg, ac
reduct

(Choi
bindin
treatin

(Choi
pathwa
decrea
displa

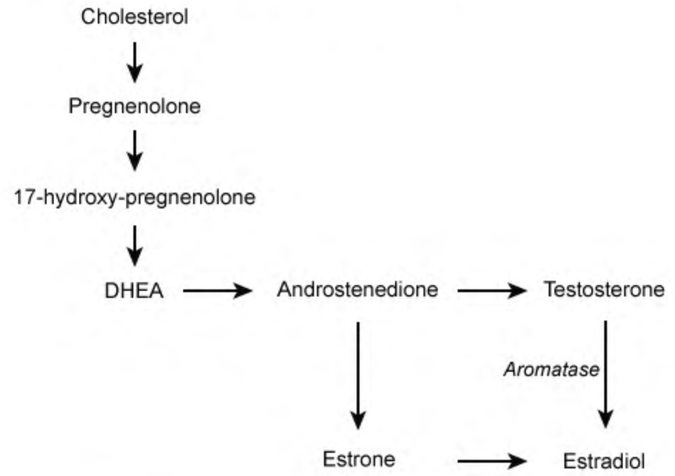
(Choi
(eg, ar
resulti
rarely

Educa
5-alph
They b
conve

References

Exhibit Display

Estrogen synthesis



DHEA = dehydroepiandrosterone.

©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

Gynecomastia is the abnormal development of glandular breast tissue in males. It is characterized by ductal epithe
promo

This p
prosta
These
testos

Howev
(eg, ac
reduct

(Choi
bindin
treatin

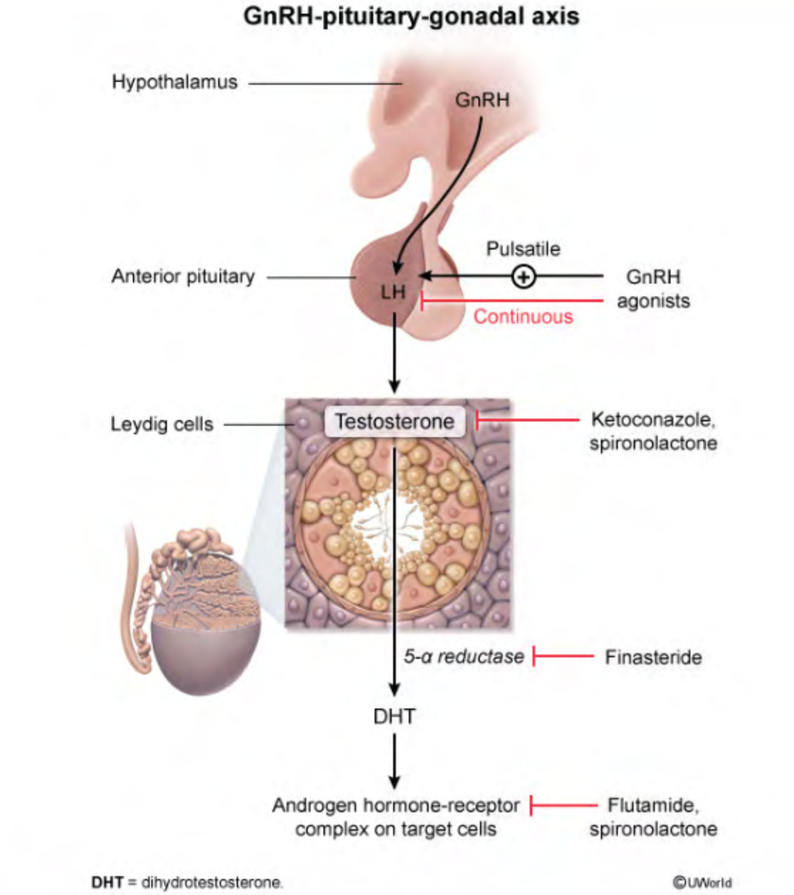
(Choi
pathw
decrea
displa

(Choi
(eg, ar
resulti
rarely

Educa
5-alph
They b
conve

References

Exhibit Display



https://t.me/USMLEWorldStep1

Gynecomastia is the abnormal development of glandular breast tissue in males. It is characterized by ductal epithe
promo

This p
prosta
These
testos

Howev
(eg, ac
reduct

(Choi
bindin
treatin

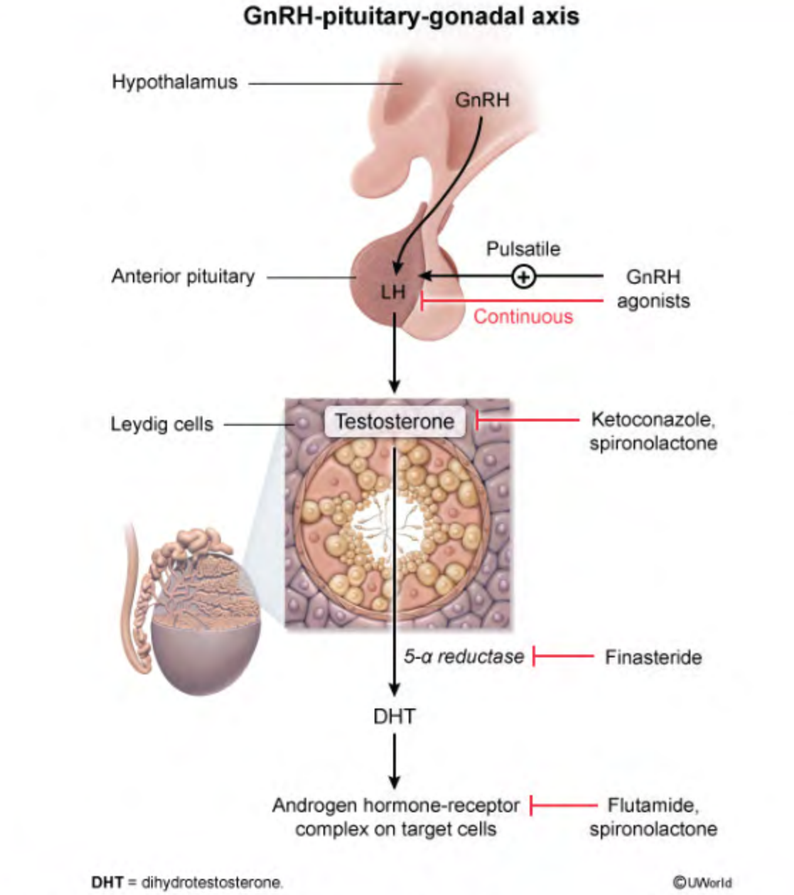
(Choi
pathw
decrea
displa

(Choi
(eg, ar
resulti
rarely

Educa
5-alph
They b
conve

References

Exhibit Display



https://t.me/USMLEWorldStep1

Gynecomastia is the abnormal development of glandular breast tissue in males. It is characterized by ductal epithe
promo

This p
prosta
These
testos

Howev
(eg, ac
reduct

(Choi
bindin
treatin

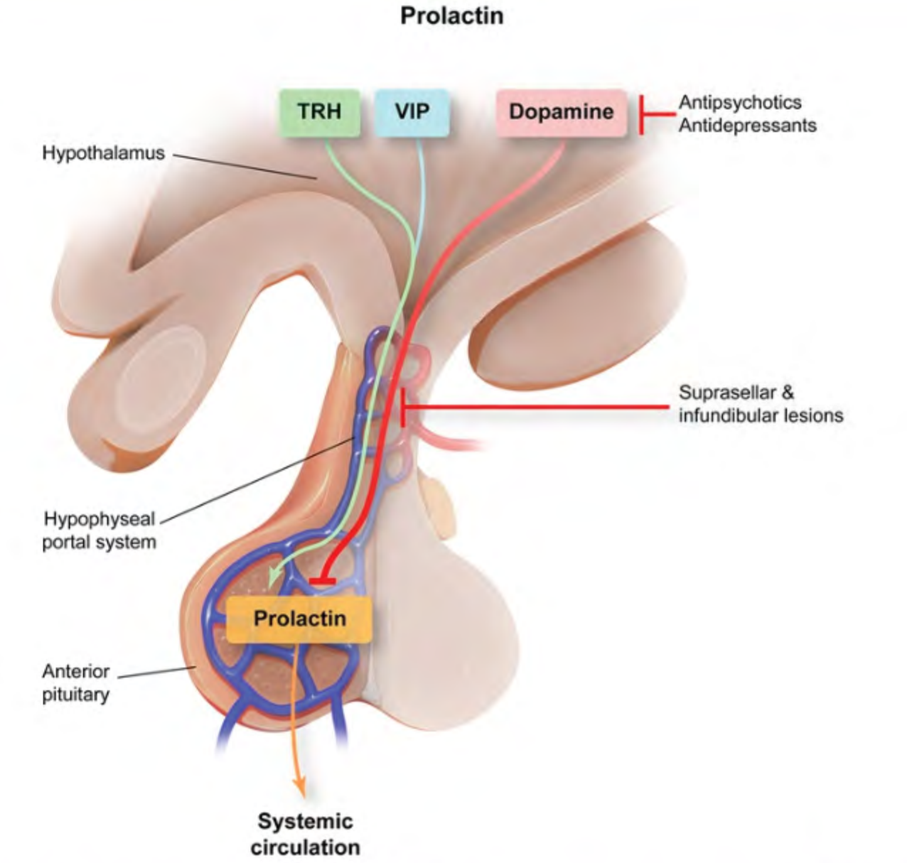
(Choi
pathw
decrea
displa

(Choi
(eg, ar
resulti
rarely

Educa
5-alph
They b
conve

References

Exhibit Display



Zoom In Zoom Out Reset New | Existing My Notebook

https://t.me/USMLEWorldStep1

Gynecomastia is the abnormal development of glandular breast tissue in males. It is characterized by ductal epithe
promo

This p
prosta
These
testos

Howev
(eg, ac
reduct

(Choi
bindin
treatin

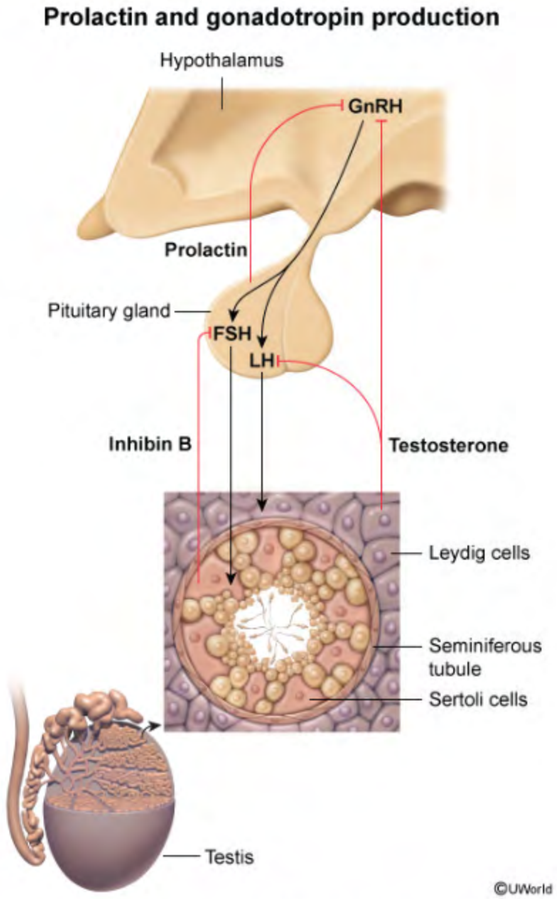
(Choi
pathw
decrea
displa

(Choi
(eg, ar
resulti
rarely

Educa
5-alph
They b
conve

References

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

A 32-year-old man is evaluated for recurrent nausea and vomiting. The patient has nausea and upper abdominal discomfort after meals and feels full even after eating a small amount of food. He also has experienced several episodes of vomiting of undigested food particles but has had no fever or diarrhea. The patient has a history of type 1 diabetes mellitus and diabetic neuropathy. Physical examination shows a clear oropharynx. The abdomen is soft, nondistended, and nontender with no organomegaly. Bowel sounds are normoactive. Stool testing for occult blood is negative. Upper gastrointestinal endoscopy reveals no abnormalities. Treatment with an oral medication is initiated, but it is stopped after the patient experiences abnormal involuntary movements. A macrolide antibiotic is prescribed, which improves his symptoms. Which of following mechanisms is most likely responsible for the improvement in this patient's symptoms?

- A. Agonistic activity on motilin receptors
- B. Blockade of gastrointestinal muscarinic receptors
- C. Increase in intestinal fluid secretion
- D. Protective effect on gastric mucosa
- E. Suppression of intestinal bacterial growth

Submit

https://t.me/USMLEWorldStep1

A 32-year-old man is evaluated for recurrent nausea and vomiting. The patient has nausea and upper abdominal discomfort after meals and feels full even after eating a small amount of food. He also has experienced several episodes of vomiting of undigested food particles but has had no fever or diarrhea. The patient has a history of type 1 diabetes mellitus and diabetic neuropathy. Physical examination shows a clear oropharynx. The abdomen is soft, nondistended, and nontender with no organomegaly. Bowel sounds are normoactive. Stool testing for occult blood is negative. Upper gastrointestinal endoscopy reveals no abnormalities. Treatment with an oral medication is initiated, but it is stopped after the patient experiences abnormal involuntary movements. A macrolide antibiotic is prescribed, which improves his symptoms. Which of following mechanisms is most likely responsible for the improvement in this patient's symptoms?

- ✓ A. Agonistic activity on motilin receptors (63%)
- ✗ B. Blockade of gastrointestinal muscarinic receptors (6%)
- C. Increase in intestinal fluid secretion (2%)
- D. Protective effect on gastric mucosa (3%)
- E. Suppression of intestinal bacterial growth (23%)

Incorrect
Correct answer
A

63%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

This patient with diabetes mellitus has postprandial nausea, vomiting of undigested food, bloating, and early satiety, raising strong suspicion for **diabetic gastroparesis**, an autonomic neuropathy of the gastrointestinal tract marked by delayed gastric emptying in the absence of mechanical obstruction (eg, normal esophagogastroduodenoscopy [EGD]). Metoclopramide, a dopamine 2 receptor antagonist, can improve symptoms but is occasionally associated with extrapyramidal side effects (eg, dystonia) and tardive dyskinesia (eg, involuntary movements)

https://t.me/USMLEWorldStep1

This patient with diabetes mellitus has postprandial nausea, vomiting of undigested food, bloating, and early satiety, raising strong suspicion for **diabetic gastroparesis**, an autonomic neuropathy of the gastrointestinal tract marked by delayed gastric emptying in the absence of mechanical obstruction (eg, normal esophagogastroduodenoscopy [EGD]). Metoclopramide, a dopamine 2 receptor antagonist, can improve symptoms but is occasionally associated with extrapyramidal side effects (eg, dystonia) and tardive dyskinesia (eg, involuntary movements).

For patients with gastroparesis who cannot tolerate metoclopramide, **erythromycin**, a macrolide antibiotic, can be used as an alternate prokinetic agent. The prokinetic effects of erythromycin stem from the **activation of the motilin receptor** in the smooth muscle of the upper digestive tract, which results in coordinated peristaltic contractions that begin in the stomach and move through the entire upper digestive system (thereby propelling food into the colon).

When used as an antibiotic, erythromycin can cause significant abdominal cramping, but in the setting of gastroparesis, the prokinetic effects can be leveraged to improve gastric emptying and ameliorate gastroparesis symptoms. However, the agonist effects of erythromycin diminish over time (tachyphylaxis) so it is generally used for short periods (<4 weeks).

(Choices B and C) Patients with irritable bowel syndrome (IBS) who have significant gastrointestinal bloating symptoms can be treated with antispasmodic medications (eg, dicycloverine) that block gastrointestinal muscarinic receptors. Those with constipation-predominant IBS are sometimes treated with lubiprostone, a chloride channel activator, to increase intestinal fluid secretion. IBS is usually marked by periods of diarrhea and/or constipation and abdominal bloating; early satiety and vomiting of undigested food would be atypical.

(Choice D) Peptic ulcer disease (PUD) is treated with medications (eg, proton pump inhibitor, sucralfate) that have a protective effect on the gastrointestinal mucosa. Although PUD can occasionally cause nausea, vomiting, and early satiety due to gastric outlet obstruction, most patients have significant upper abdominal pain. In addition, an EGD would show a gastric or duodenal ulcer.

(Choice E) Patients with small intestinal bacterial overgrowth (SIBO)—colonization of the small intestine with colonic bacteria—often develop bloating, abdominal discomfort, flatulence, and/or diarrhea. However, early satiety and vomiting of undigested food would be atypical. In addition, SIBO is generally treated with rifaximin or

https://t.me/USMLEWorldStep1

used as an alternate prokinetic agent. The prokinetic effects of erythromycin stem from the **activation of the motilin receptor** in the smooth muscle of the upper digestive tract, which results in coordinated peristaltic contractions that begin in the stomach and move through the entire upper digestive system (thereby propelling food into the colon).

When used as an antibiotic, erythromycin can cause significant abdominal cramping, but in the setting of gastroparesis, the prokinetic effects can be leveraged to improve gastric emptying and ameliorate gastroparesis symptoms. However, the agonist effects of erythromycin diminish over time (tachyphylaxis) so it is generally used for short periods (<4 weeks).

(Choices B and C) Patients with irritable bowel syndrome (IBS) who have significant gastrointestinal bloating symptoms can be treated with antispasmodic medications (eg, dicycloverine) that block gastrointestinal muscarinic receptors. Those with constipation-predominant IBS are sometimes treated with lubiprostone, a chloride channel activator, to increase intestinal fluid secretion. IBS is usually marked by periods of diarrhea and/or constipation and abdominal bloating; early satiety and vomiting of undigested food would be atypical.

(Choice D) Peptic ulcer disease (PUD) is treated with medications (eg, proton pump inhibitor, sucralfate) that have a protective effect on the gastrointestinal mucosa. Although PUD can occasionally cause nausea, vomiting, and early satiety due to gastric outlet obstruction, most patients have significant upper abdominal pain. In addition, an EGD would show a gastric or duodenal ulcer.

(Choice E) Patients with small intestinal bacterial overgrowth (SIBO)—colonization of the small intestine with colonic bacteria—often develop bloating, abdominal discomfort, flatulence, and/or diarrhea. However, early satiety and vomiting of undigested food would be atypical. In addition, SIBO is generally treated with rifaximin or neomycin.

Educational objective:
Erythromycin stimulates upper gastrointestinal motility by acting as an agonist on motilin receptors in the muscularis externa. Therefore, it can be used to treat gastroparesis (ie, delayed gastric emptying), a condition that frequently occurs in patients with long standing diabetes mellitus.

Pharmacology Endocrine, Diabetes & Metabolism Gastroparesis

https://t.me/USMLEWorldStep1

A 25-year-old woman comes to the office due to excessive facial hair growth that has worsened over the past several years. The patient is very concerned and says it makes her feel self-conscious in public. She has tried several cosmetic measures, including laser removal and waxing, but the results have been unsatisfactory. Her past medical history is insignificant, and she takes no medications. The patient's last menstrual period was 6 weeks ago, but she regularly has long cycles and otherwise feels well. She is sexually active with her boyfriend and uses condoms for contraception. Examination shows moderate obesity with mild hirsutism on the face and chest. The patient is initiated on a combination oral contraceptive. Which of the following describes the primary mechanism by which this agent reduces hirsutism?

- A. Blockade of ornithine decarboxylase
- B. Decreased androgen production
- C. Increased insulin sensitivity
- D. Inhibition of 5-α-reductase
- E. Inhibition of androgen receptors

Submit

https://t.me/USMLEWorldStep1

A 25-year-old woman comes to the office due to excessive facial hair growth that has worsened over the past several years. The patient is very concerned and says it makes her feel self-conscious in public. She has tried several cosmetic measures, including laser removal and waxing, but the results have been unsatisfactory. Her past medical history is insignificant, and she takes no medications. The patient's last menstrual period was 6 weeks ago, but she regularly has long cycles and otherwise feels well. She is sexually active with her boyfriend and uses condoms for contraception. Examination shows moderate obesity with mild hirsutism on the face and chest. The patient is initiated on a combination oral contraceptive. Which of the following describes the primary mechanism by which this agent reduces hirsutism?

- A. Blockade of ornithine decarboxylase (0%)
- ✓ B. Decreased androgen production (80%)
- C. Increased insulin sensitivity (1%)
- D. Inhibition of 5-α-reductase (6%)
- E. Inhibition of androgen receptors (10%)

Correct

80% Answered correctly

03 secs Time Spent

2023 Version

Explanation

Polycystic ovary syndrome	
Clinical features	• Androgen excess: hirsutism, acne, androgenic alopecia • Ovarian dysfunction: menstrual irregularity, polycystic ovaries • Insulin resistance: acanthosis nigricans

https://t.me/USMLEWorldStep1

Explanation

Polycystic ovary syndrome	
Clinical features	• Androgen excess: hirsutism, acne, androgenic alopecia • Ovarian dysfunction: menstrual irregularity, polycystic ovaries • Insulin resistance: acanthosis nigricans, glucose intolerance/diabetes, metabolic syndrome • Obesity
Treatment	• Weight loss • Combination hormonal contraceptives • Metformin (if hyperglycemia/diabetes)

Excessive male-pattern hair growth in a woman is called **hirsutism**. Hirsutism can be due to increased androgen production (eg, polycystic ovary syndrome, Cushing syndrome, ovarian and adrenal tumors), increased local conversion of testosterone to dihydrotestosterone (DHT), or higher sensitivity of hair follicles to DHT (eg, idiopathic hirsutism). With excessive androgen exposure, soft, non-pigmented villous hair changes to coarse pigmented terminal hair in androgen-dependent areas of the body (eg, face, chest, back). **Virilization** occurs with very high androgen levels and is characterized by clitoromegaly, increased muscularity, and voice deepening in addition to hirsutism.

The most common cause of hirsutism is **polycystic ovary syndrome** (PCOS), which is often associated with elevated androgen levels. Combination oral contraceptive pills (OCPs) are usually the first choice for treating hirsutism in PCOS. OCPs work by suppressing LH secretion from the pituitary, thereby decreasing ovarian androgen production. They also increase sex hormone-binding globulin synthesis by the liver, decreasing free testosterone levels.

https://t.me/USMLEWorldStep1

- Metformin (if hyperglycemia/diabetes)

Excessive male-pattern hair growth in a woman is called **hirsutism**. Hirsutism can be due to increased androgen production (eg, polycystic ovary syndrome, Cushing syndrome, ovarian and adrenal tumors), increased local conversion of testosterone to dihydrotestosterone (DHT), or higher sensitivity of hair follicles to DHT (eg, idiopathic hirsutism). With excessive androgen exposure, soft, non-pigmented villous hair changes to coarse pigmented terminal hair in androgen-dependent areas of the body (eg, face, chest, back). **Virilization** occurs with very high androgen levels and is characterized by clitoromegaly, increased muscularity, and voice deepening in addition to hirsutism.

The most common cause of hirsutism is **polycystic ovary syndrome** (PCOS), which is often associated with elevated androgen levels. Combination oral contraceptive pills (OCPs) are usually the first choice for treating hirsutism in PCOS. OCPs work by suppressing LH secretion from the pituitary, thereby decreasing ovarian androgen production. They also increase sex hormone-binding globulin synthesis by the liver, decreasing free testosterone levels.

(Choice A) Ornithine decarboxylase is involved in DNA stabilization and repair. Inhibition leads to decreased cell growth and increased apoptosis. Eflornithine is a topical ornithine decarboxylase inhibitor used to decrease the rate of facial hair growth.

(Choice C) Patients with PCOS who develop diabetes mellitus are usually treated with metformin, which increases insulin sensitivity. Metformin can also help normalize menses but would not improve hirsutism.

(Choices D and E) Testosterone receptor antagonists (eg, spironolactone) are effective in suppressing androgen-dependent hair growth. 5-α-reductase inhibitors (eg, finasteride) decrease peripheral conversion of testosterone to DHT but are less effective than testosterone receptor antagonists in treating hirsutism. Both are strongly teratogenic.

Educational objective:
Male-pattern hair growth in a woman is called hirsutism; the most common cause is polycystic ovary syndrome. Combination oral contraceptive pills can treat hirsutism by suppressing pituitary LH secretion and subsequently decreasing ovarian androgen production.

References

https://t.me/USMLEWorldStep1

A 1-week-old newborn is seen for abnormal thyroid function tests that were performed as part of routine screening. Serum thyroxine (T4) was low and serum TSH was normal. The patient was born by spontaneous vaginal delivery at 40 weeks of gestation to a 28-year-old primigravida. During the pregnancy, the mother took acetaminophen intermittently for low back pain. Examination of the newborn shows no abnormal findings. Repeat thyroid function test results are as follows:

Free T4	1.2 µg/dL (normal: 0.8-1.95)
Total T4	4 µg/dL
TSH	3 µU/mL

Which of the following is the most likely cause of the patient's abnormal thyroid function tests?

- A. Decreased T4 to triiodothyronine conversion
- B. Deficiency of thyroxine-binding globulin
- C. Hypoalbuminemia
- D. Hypopituitarism
- E. Thyroid dysgenesis

Submit

https://t.me/USMLEWorldStep1

A 1-week-old newborn is seen for abnormal thyroid function tests that were performed as part of routine screening. Serum thyroxine (T4) was low and serum TSH was normal. The patient was born by spontaneous vaginal delivery at 40 weeks of gestation to a 28-year-old primigravida. During the pregnancy, the mother took acetaminophen intermittently for low back pain. Examination of the newborn shows no abnormal findings. Repeat thyroid function test results are as follows:

Free T4	1.2 µg/dL (normal: 0.8-1.95)
Total T4	4 µg/dL
TSH	3 µU/mL

Which of the following is the most likely cause of the patient's abnormal thyroid function tests?

- A. Decreased T4 to triiodothyronine conversion (10%)
- ✓ B. Deficiency of thyroxine-binding globulin (59%)
- C. Hypoalbuminemia (8%)
- D. Hypopituitarism (4%)
- E. Thyroid dysgenesis (18%)

Correct

59% Answered correctly

03 secs Time Spent

2023 Version

Explanation



https://t.me/USMLEWorldStep1

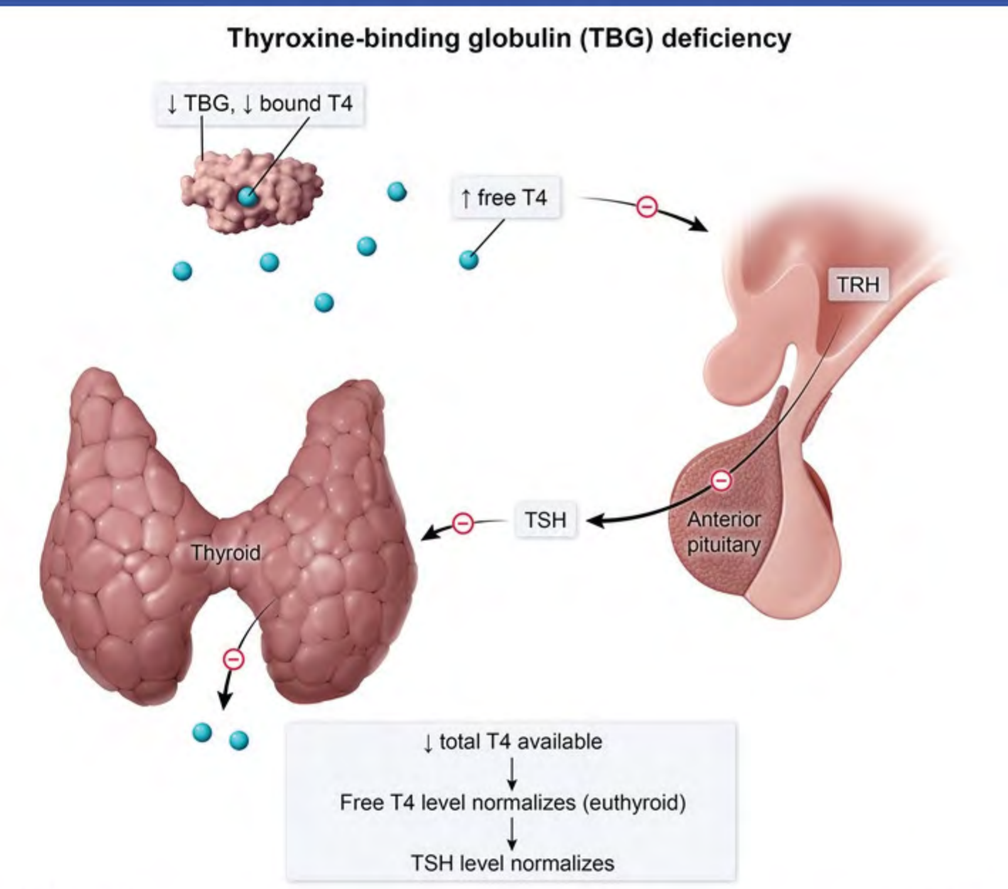
Correct

59%
Answered correctly

03 secs
Time Spent

2023
Version

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

This neonate with a low total thyroxine (T4) but normal free T4 and normal TSH likely has a **deficiency** of **thyroxine-binding globulin** (TBG). Congenital TBG deficiency is a **benign**, X-linked disorder usually identified on

https://t.me/USMLEWorldStep1

T4 = thyroxine.

©UWorld

This neonate with a low total thyroxine (T4) but normal free T4 and normal TSH likely has a **deficiency** of **thyroxine-binding globulin** (TBG). Congenital TBG deficiency is a **benign**, X-linked disorder usually identified on newborn screening.

In general, the majority of circulating T4 is bound to TBG, which then serves as a storage pool to replenish the biologically active free T4 that is continuously cleared by the kidneys. Therefore, TBG helps **maintain a constant free T4 level**.

When TBG is deficient, less T4 is bound and a greater proportion is allowed to freely circulate. **Total T4 is low** due to the decrease in bound T4 fraction. However, since physiologic feedback is intact, **TSH and free T4 levels remain normal**. Because the levels of active (free) thyroid hormone are normal, patients are clinically **euthyroid** and asymptomatic, so **no treatment** is required.

(Choice A) Certain placentally transferred maternal medications (eg, propylthiouracil) decrease conversion of T4 to triiodothyronine (T3), causing transient neonatal hypothyroidism (ie, low T4, high TSH). Acetaminophen does not interfere with thyroid hormone synthesis.

(Choice C) Because only a small percentage of T4 is bound to albumin, hypoalbuminia does not significantly affect thyroid hormone levels. In addition, this patient has no risk factors for hypoalbuminemia (eg, malnutrition, sepsis, gastrointestinal/renal loss).

(Choice D) Hypopituitarism causes central hypothyroidism, which is characterized by low TSH, total T4, and free T4. Other midline defects (eg, cleft lip) or hormonal imbalances (eg, hypoglycemia due to ACTH deficiency) are often present.

(Choice E) Thyroid dysgenesis (eg, ectopy, hypoplasia) is the most common cause of congenital hypothyroidism, which is usually asymptomatic at birth. In contrast to this case, laboratory findings include high TSH and low total and free T4.

Educational objective:
Thyroxine-binding globulin deficiency is a benign disorder characterized by low total thyroxine (T4) and normal free T4 and TSH levels. Patients are euthyroid and do not require treatment.

https://t.me/USMLEWorldStep1

T4 = thyroxine.

©UWorld

This neonate with a low total thyroxine (T4) but normal free T4 and normal TSH likely has a **deficiency** of **thyrox**
newbo

In gen
biologi
free T

When
to the
remai
and as

(Choi
to triio
not int

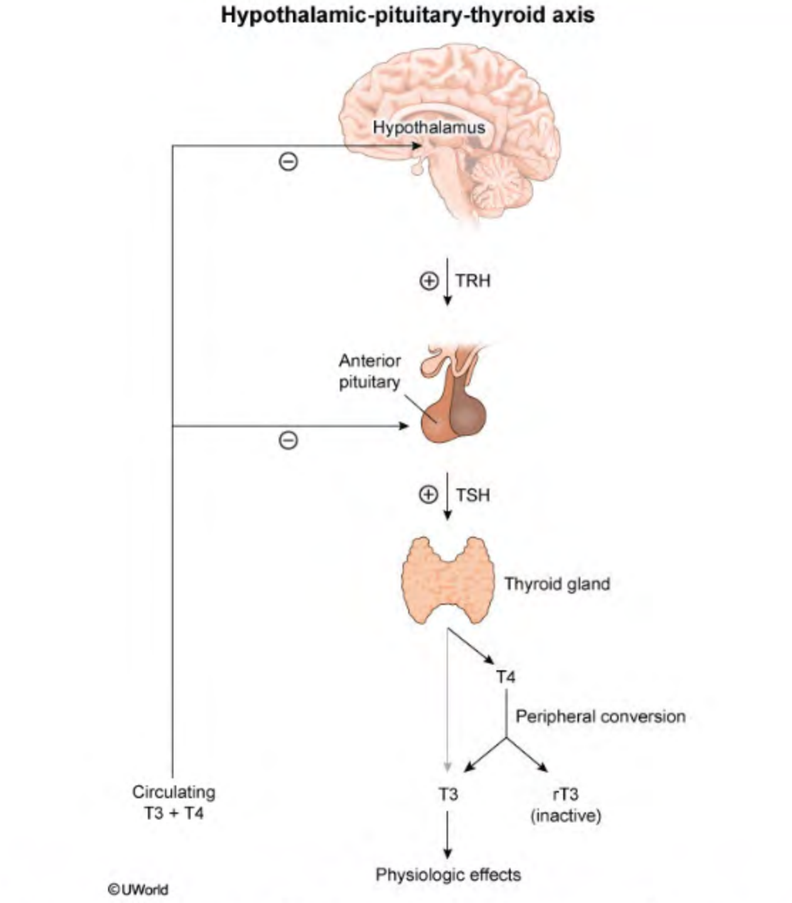
(Choi
affect
sepsis

(Choi
T4. O
often p

(Choi
which
and fre

Educa
Thyrox
T4 and TSH levels. Patients are euthyroid and do not require treatment.

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

A 14-year-old boy is brought to the office due to painless nodules on his lips and tongue. The lesions appeared several months ago and have been progressively enlarging. The patient underwent total thyroidectomy 5 years ago following the discovery of a thyroid mass and takes replacement thyroid hormone. On physical examination, the patient is tall and slender with disproportionately long arms and legs. His fingers are also long and thin, and joint laxity is present. Eye examination is normal and oral inspection reveals several small, soft, flesh-colored papules on his lips and tongue. Serum TSH is within normal limits. This patient most likely has which of the following conditions?

- A. Ehlers-Danlos syndrome
- B. Marfan syndrome
- C. Multiple endocrine neoplasia type 1
- D. Multiple endocrine neoplasia type 2B
- E. Neurofibromatosis type 1
- F. Neurofibromatosis type 2

Submit

https://t.me/USMLEWorldStep1

A 14-year-old boy is brought to the office due to painless nodules on his lips and tongue. The lesions appeared several months ago and have been progressively enlarging. The patient underwent total thyroidectomy 5 years ago following the discovery of a thyroid mass and takes replacement thyroid hormone. On physical examination, the patient is tall and slender with disproportionately long arms and legs. His fingers are also long and thin, and joint laxity is present. Eye examination is normal and oral inspection reveals several small, soft, flesh-colored papules on his lips and tongue. Serum TSH is within normal limits. This patient most likely has which of the following conditions?

- A. Ehlers-Danlos syndrome (8%)
- ✗ B. Marfan syndrome (13%)
- C. Multiple endocrine neoplasia type 1 (4%)
- ✓ D. Multiple endocrine neoplasia type 2B (67%)
- E. Neurofibromatosis type 1 (4%)
- F. Neurofibromatosis type 2 (1%)

Incorrect
Correct answer
D

67%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

Classification of multiple endocrine neoplasia	
Type 1	• **Primary hyperparathyroidism** (parathyroid adenomas or hyperplasia) • Pituitary tumors (prolactin, visual defects) • Pancreatic tumors (especially gastrinomas)

https://t.me/USMLEWorldStep1

Classification of multiple endocrine neoplasia	
Type 1	• **Primary hyperparathyroidism** (parathyroid adenomas or hyperplasia) • Pituitary tumors (prolactin, visual defects) • Pancreatic tumors (especially gastrinomas)
Type 2A	• **Medullary thyroid cancer** (calcitonin) • Pheochromocytoma • Primary hyperparathyroidism (parathyroid hyperplasia)
Type 2B	• **Medullary thyroid cancer** (calcitonin) • Pheochromocytoma • Mucosal neuromas/marfanoid habitus

This patient has a **marfanoid habitus**—a tall and slender build with disproportionately long arms, legs, and fingers. The flesh-colored nodules on his lips and tongue are likely **mucosal neuromas**, which are unencapsulated, thickened proliferations of neural tissue. This patient also has a history of total thyroidectomy, which was likely due to **medullary thyroid cancer** (MTC). This combination of clinical findings is consistent with **multiple endocrine neoplasia type 2B** (MEN 2B), which is due to an autosomal dominant germ-line mutation in the *RET* proto-oncogene.

Other possible manifestations of MEN 2B include **pheochromocytoma** and intestinal ganglioneuromas (which may cause constipation). The earliest manifestations of the disease often appear in childhood or adolescence. Early recognition of MEN 2B is important as almost all patients develop MTC and prophylactic thyroidectomy can be life-saving.

(Choice A) Ehlers-Danlos syndrome is a heritable connective tissue disorder characterized by skin hyperextensibility, joint hypermobility, tissue fragility, poor wound healing, and easy bruising. There is no known association between Ehlers-Danlos syndrome and thyroid cancer or perioral nodules.

https://t.me/USMLEWorldStep1

2B	• Mucosal neuromas/marfanoid habitus

This patient has a **marfanoid habitus**—a tall and slender build with disproportionately long arms, legs, and fingers. The flesh-colored nodules on his lips and tongue are likely **mucosal neuromas**, which are unencapsulated, thickened proliferations of neural tissue. This patient also has a history of total thyroidectomy, which was likely due to **medullary thyroid cancer** (MTC). This combination of clinical findings is consistent with **multiple endocrine neoplasia type 2B** (MEN 2B), which is due to an autosomal dominant germ-line mutation in the *RET* proto-oncogene.

Other possible manifestations of MEN 2B include **pheochromocytoma** and intestinal ganglioneuromas (which may cause constipation). The earliest manifestations of the disease often appear in childhood or adolescence. Early recognition of MEN 2B is important as almost all patients develop MTC and prophylactic thyroidectomy can be life-saving.

(Choice A) Ehlers-Danlos syndrome is a heritable connective tissue disorder characterized by skin hyperextensibility, joint hypermobility, tissue fragility, poor wound healing, and easy bruising. There is no known association between Ehlers-Danlos syndrome and thyroid cancer or perioral nodules.

(Choice B) Although this patient has a marfanoid habitus, the remainder of his presentation is more consistent with MEN 2B than Marfan syndrome. In addition, unlike true Marfan syndrome, patients with MEN 2B do not develop aortic malformations (eg, dilation) or ocular malformations (eg, ectopia lentis).

(Choice C) Multiple endocrine neoplasia type 1 (MEN 1) is an autosomal dominant condition characterized by parathyroid adenomas with hyperparathyroidism, anterior pituitary gland tumors, and pancreatic endocrine tumors (the "3 Ps"). MEN 1 is not associated with thyroid cancer or perioral nodules.

(Choices E and F) Neurofibromatosis type 1 is characterized by café au lait spots, cutaneous neurofibromas, axillary or inguinal freckling, optic glioma, and iris hamartomas. Neurofibromatosis type 2 (the more central form) is characterized by bilateral acoustic neuromas, brain meningiomas, and schwannomas of the dorsal roots in the spinal cord. Although this patient has (mucosal) neuromas, the remainder of his presentation is more consistent with MEN 2B.

Educational objective:

https://t.me/USMLEWorldStep1

unencapsulated, thickened proliferations of neural tissue. This patient also has a history of total thyroidectomy, which was likely due to **medullary thyroid cancer** (MTC). This combination of clinical findings is consistent with **multiple endocrine neoplasia type 2B** (MEN 2B), which is due to an autosomal dominant germ-line mutation in the *RET* proto-oncogene.

Other possible manifestations of MEN 2B include **pheochromocytoma** and intestinal ganglioneuromas (which may cause constipation). The earliest manifestations of the disease often appear in childhood or adolescence. Early recognition of MEN 2B is important as almost all patients develop MTC and prophylactic thyroidectomy can be life-saving.

(Choice A) Ehlers-Danlos syndrome is a heritable connective tissue disorder characterized by skin hyperextensibility, joint hypermobility, tissue fragility, poor wound healing, and easy bruising. There is no known association between Ehlers-Danlos syndrome and thyroid cancer or perioral nodules.

(Choice B) Although this patient has a marfanoid habitus, the remainder of his presentation is more consistent with MEN 2B than Marfan syndrome. In addition, unlike true Marfan syndrome, patients with MEN 2B do not develop aortic malformations (eg, dilation) or ocular malformations (eg, ectopia lentis).

(Choice C) Multiple endocrine neoplasia type 1 (MEN 1) is an autosomal dominant condition characterized by parathyroid adenomas with hyperparathyroidism, anterior pituitary gland tumors, and pancreatic endocrine tumors (the "3 Ps"). MEN 1 is not associated with thyroid cancer or perioral nodules.

(Choices E and F) Neurofibromatosis type 1 is characterized by café au lait spots, cutaneous neurofibromas, axillary or inguinal freckling, optic glioma, and iris hamartomas. Neurofibromatosis type 2 (the more central form) is characterized by bilateral acoustic neuromas, brain meningiomas, and schwannomas of the dorsal roots in the spinal cord. Although this patient has (mucosal) neuromas, the remainder of his presentation is more consistent with MEN 2B.

Educational objective:
Multiple endocrine neoplasia type 2B is characterized by medullary thyroid cancer, pheochromocytoma, marfanoid habitus, and oral and intestinal mucosal neuromas.

Pathology Endocrine, Diabetes & Metabolism Multiple endocrine neoplasia

https://t.me/USMLEWorldStep1

hyperplasia)

Exhibit Display

Mucosal neuromas



*Associated with multiple endocrine neoplasia type 2B (MEN 2B).

©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

This p
fingers
unenc
which
multip
the *RE*

Other
may c
Early
be life-

(Choi
hypere
associ

(Choi
with M
develo

(Choi
parath
(the "3

(Choi
axillary or inguinal freckling, optic glioma, and iris hamartomas. Neurofibromatosis type 2 (the more central form) is characterized by bilateral acoustic neuromas, brain meningiomas, and schwannomas of the dorsal roots in the

https://t.me/USMLEWorldStep1

unencapsulated, thickened proliferations of neural tissue. This patient also has a history of total thyroidectomy,

which

multip

the *RE*

Other

may c

Early

be life-

(Choi

hypere

associ

(Choi

with M

develo

(Choi

parath

(the "3

(Choi

axillary

charac

spinal

with M

Educa

Multipl

habitu

Exhibit Display

Neurofibromatosis type 1



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Pathology Endocrine, Diabetes & Metabolism Multiple endocrine neoplasia

https://t.me/USMLEWorldStep1

Fifty obese adults without diabetes mellitus are enrolled in a 10-week weight loss program. The program includes a low-calorie diet and moderate-intensity exercise for at least 150 minutes per week. The study subjects who are adherent to the regimen lose an average of 7 kg (15.5 lb) at the end of 10 weeks. Venous blood samples to study biochemical changes induced by weight loss are taken at the start of the trial and at the 10-week follow-up visit. Which of the following hormonal changes are likely to occur during the course of the study?

	Ghrelin	Leptin	Insulin
A.	↑	↓	↓
B.	↓	↓	↓
C.	↓	↑	↑
D.	↑	↓	↑
E.	↑	↑	↓

Submit

https://t.me/USMLEWorldStep1

Fifty obese adults without diabetes mellitus are enrolled in a 10-week weight loss program. The program includes a low-calorie diet and moderate-intensity exercise for at least 150 minutes per week. The study subjects who are adherent to the regimen lose an average of 7 kg (15.5 lb) at the end of 10 weeks. Venous blood samples to study biochemical changes induced by weight loss are taken at the start of the trial and at the 10-week follow-up visit. Which of the following hormonal changes are likely to occur during the course of the study?

	Ghrelin	Leptin	Insulin	
✓ A.	↑	↓	↓	(44%)
✗ B.	↓	↓	↓	(11%)
C.	↓	↑	↑	(28%)
D.	↑	↓	↑	(8%)
E.	↑	↑	↓	(6%)

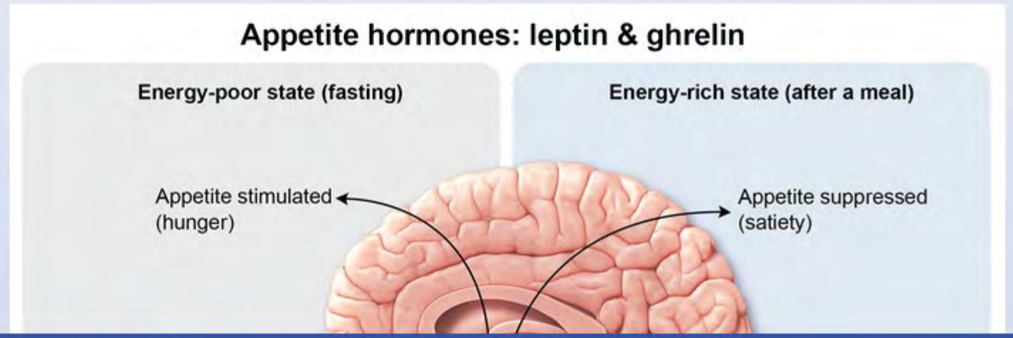
Incorrect
Correct answer
A

44%
Answered correctly

06 secs
Time Spent

2023
Version

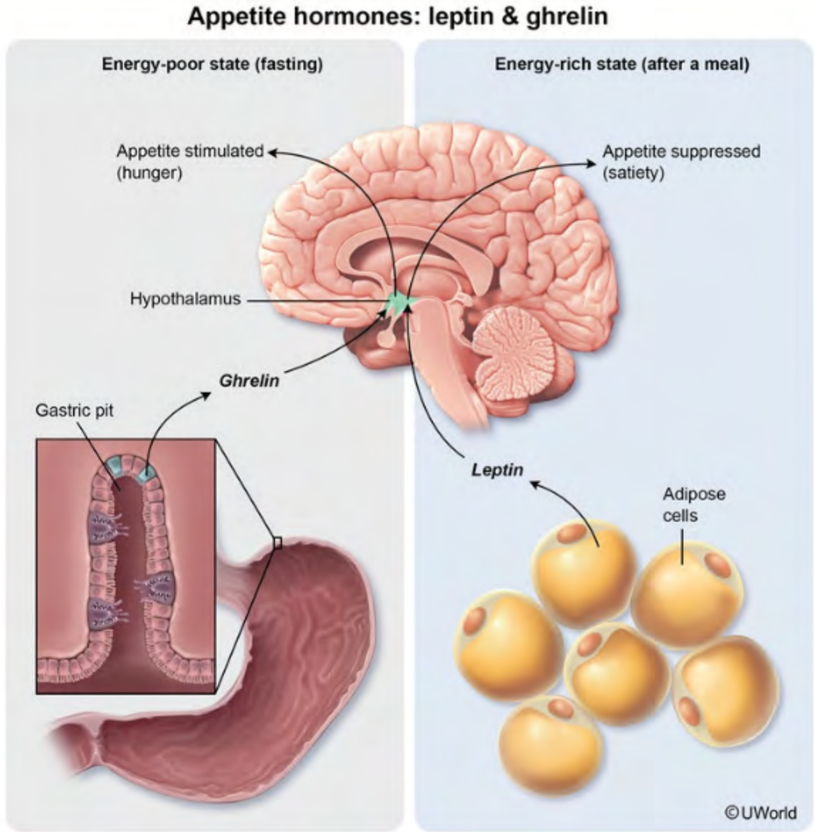
Explanation



https://t.me/USMLEWorldStep1

Fifty obese adults without diabetes mellitus are enrolled in a 10-week weight loss program. The program includes a low-
adhere
bioche
Which

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1



©UWorld

Energy homeostasis and body fat content are regulated by a complex network of hormones. Prominent hormones involved in weight regulation include:

- **Ghrelin:** Produced primarily in the stomach in response to fasting, ghrelin stimulates appetite and promotes weight gain.
- **Leptin:** Produced primarily by fat cells in response to short-term food intake and long-term adequacy of fat stores, leptin acts on the hypothalamus to decrease appetite (obesity blunts this action). During fasting states, leptin levels fall.
- **Insulin:** Produced by pancreatic beta cells in response to high blood glucose levels, insulin acts on the CNS to decrease appetite, in addition to its effects on glucose metabolism. Levels are higher and effects are blunted in obesity (insulin resistance); weight loss is associated with greater insulin sensitivity and lower insulin levels.

Caloric restriction and falling fat stores, as in these study subjects, lead to **increased ghrelin** levels along with **decreased insulin and leptin** levels. This causes an increase in appetite and, typically, regain of weight. The effect can last up to a year or more and accounts for much of the difficulty patients have in maintaining short-term weight loss.

(Choice B) Certain bariatric procedures that alter stomach capacity (eg, sleeve gastrectomy) can induce weight loss with decreased ghrelin production (may reduce weight loss-associated appetite stimulation). However, dietary modification and exercise alone would lead to increased ghrelin secretion.

(Choice C) Overeating and weight gain suppress ghrelin secretion and increase secretion of leptin and insulin.

(Choice D) HIV-associated lipodystrophy is an alteration in fat distribution, most often seen in patients receiving highly active antiretroviral therapy. Numerous metabolic abnormalities have been seen in this disorder, including increased insulin levels, increased ghrelin, and decreased leptin secretion.

(Choice E) Fasting states that stimulate ghrelin and suppress insulin secretion generally lead to lower, not higher, leptin levels.

https://t.me/USMLEWorldStep1

- **Leptin:** Produced primarily by fat cells in response to short-term food intake and long-term adequacy of fat stores, leptin acts on the hypothalamus to decrease appetite (obesity blunts this action). During fasting states, leptin levels fall.
- **Insulin:** Produced by pancreatic beta cells in response to high blood glucose levels, insulin acts on the CNS to decrease appetite, in addition to its effects on glucose metabolism. Levels are higher and effects are blunted in obesity (insulin resistance); weight loss is associated with greater insulin sensitivity and lower insulin levels.

Caloric restriction and falling fat stores, as in these study subjects, lead to **increased ghrelin** levels along with **decreased insulin and leptin** levels. This causes an increase in appetite and, typically, regain of weight. The effect can last up to a year or more and accounts for much of the difficulty patients have in maintaining short-term weight loss.

(Choice B) Certain bariatric procedures that alter stomach capacity (eg, sleeve gastrectomy) can induce weight loss with decreased ghrelin production (may reduce weight loss-associated appetite stimulation). However, dietary modification and exercise alone would lead to increased ghrelin secretion.

(Choice C) Overeating and weight gain suppress ghrelin secretion and increase secretion of leptin and insulin.

(Choice D) HIV-associated lipodystrophy is an alteration in fat distribution, most often seen in patients receiving highly active antiretroviral therapy. Numerous metabolic abnormalities have been seen in this disorder, including increased insulin levels, increased ghrelin, and decreased leptin secretion.

(Choice E) Fasting states that stimulate ghrelin and suppress insulin secretion generally lead to lower, not higher, leptin levels.

Educational objective:
Ghrelin stimulates appetite and promotes weight gain. Leptin and insulin act in the CNS to decrease appetite. Caloric restriction leads to increased ghrelin levels along with decreased insulin and leptin levels, causing an increase in appetite that can make it difficult to maintain weight loss.

References

- Long-term persistence of hormonal adaptations to weight loss.

https://t.me/USMLEWorldStep1

A 34-year-old woman comes to the office due to inability to lose weight despite diet and exercise. She reports that she gained a significant amount of weight after she stopped smoking 4 years ago. The patient has tried several commercial weight-loss diet programs in the last year without success. She wants to lose at least 4.5 kg (10 lb) over the next few months before she gets married. The patient does not have any other medical conditions and takes no medications. Blood pressure is 122/80 mm Hg and pulse is 78/min. BMI is 33 kg/m^2. Physical examination shows an obese habitus but is otherwise unremarkable. Laboratory testing for secondary causes of weight gain is unrevealing. In addition to encouraging continued efforts at lifestyle change, the physician prescribes a short course of oral phentermine for weight loss. The weight loss induced by this medication is caused by which of the following mechanisms?

- A. Delayed gastric emptying
- B. Lipase inhibition
- C. Opioid antagonist
- D. Reduced presynaptic reuptake of serotonin
- E. Release of norepinephrine

Submit

https://t.me/USMLEWorldStep1

A 34-year-old woman comes to the office due to inability to lose weight despite diet and exercise. She reports that she gained a significant amount of weight after she stopped smoking 4 years ago. The patient has tried several commercial weight-loss diet programs in the last year without success. She wants to lose at least 4.5 kg (10 lb) over the next few months before she gets married. The patient does not have any other medical conditions and takes no medications. Blood pressure is 122/80 mm Hg and pulse is 78/min. BMI is 33 kg/m^2. Physical examination shows an obese habitus but is otherwise unremarkable. Laboratory testing for secondary causes of weight gain is unrevealing. In addition to encouraging continued efforts at lifestyle change, the physician prescribes a short course of oral phentermine for weight loss. The weight loss induced by this medication is caused by which of the following mechanisms?

- A. Delayed gastric emptying (32%)
- ✗ B. Lipase inhibition (10%)
- C. Opioid antagonist (3%)
- D. Reduced presynaptic reuptake of serotonin (6%)
- ✓ E. Release of norepinephrine (46%)

Incorrect
Correct answer
E

46%
Answered correctly

04 secs
Time Spent

2023
Version

Explanation

Medications for weight loss		
	Mechanism of action	**Notable features**
Sympathomimetic amines (ie, phentermine, diethylpropion,	Stimulant/CAS	• High rate of weight regain • Not recommended for patients

https://t.me/USMLEWorldStep1

Medications for weight loss		
	Mechanism of action	**Notable features**
Sympathomimetic amines (ie, phentermine, diethylpropion, benzphetamine)	Stimulant/CAS	• High rate of weight regain • Not recommended for patients with CVD
Orlistat	Intestinal lipase inhibitor	• Significant gastrointestinal side effects
Bupropion/naltrexone	CAS (antidepressant + opioid antagonist)	• Lowers seizure threshold • May also assist in smoking cessation
CAS = central appetite suppressant; **CVD** = cardiovascular disease.		

Norepinephrine-releasing agents (eg, **phentermine**) are sympathomimetic weight-loss drugs indicated for **short-term** (≤12 weeks) treatment of obesity. They work by stimulating release and inhibiting reuptake of norepinephrine and, to a lesser extent, serotonin and dopamine. Subjective effects include an **increased** sensation of **satiety** and subsequently reduced caloric intake.

Because of the increased sympathetic activity associated with these drugs, they can raise blood pressure and should be **avoided** in patients with comorbid **hypertension** or **heart disease**. Norepinephrine-releasing agents can induce brisk initial weight loss but are notable for poor long-term benefit, and most patients regain the lost weight following discontinuation.

(Choice A) Glucagonlike peptide-1 (GLP-1) agonists (eg, liraglutide) increase glucose-dependent insulin secretion and are most commonly used in treatment of type 2 diabetes mellitus. In addition, GLP-1 agonists cause delayed gastric emptying and decreased appetite, leading to weight loss.

(Choice B) Orlistat is an intestinal lipase inhibitor. It acts by reducing the digestion and subsequent absorption of dietary fats. The increased residual fat content in the intestinal lumen can lead to intestinal discomfort, diarrhea, fecal incontinence, and impaired absorption of fat-soluble vitamins (eg, vitamin D).

https://t.me/USMLEWorldStep1

Norepinephrine-releasing agents (eg, **phentermine**) are sympathomimetic weight-loss drugs indicated for **short-term** (≤12 weeks) treatment of obesity. They work by stimulating release and inhibiting reuptake of norepinephrine and, to a lesser extent, serotonin and dopamine. Subjective effects include an **increased** sensation of **satiety** and subsequently reduced caloric intake.

Because of the increased sympathetic activity associated with these drugs, they can raise blood pressure and should be **avoided** in patients with comorbid **hypertension** or **heart disease**. Norepinephrine-releasing agents can induce brisk initial weight loss but are notable for poor long-term benefit, and most patients regain the lost weight following discontinuation.

(Choice A) Glucagonlike peptide-1 (GLP-1) agonists (eg, liraglutide) increase glucose-dependent insulin secretion and are most commonly used in treatment of type 2 diabetes mellitus. In addition, GLP-1 agonists cause delayed gastric emptying and decreased appetite, leading to weight loss.

(Choice B) Orlistat is an intestinal lipase inhibitor. It acts by reducing the digestion and subsequent absorption of dietary fats. The increased residual fat content in the intestinal lumen can lead to intestinal discomfort, diarrhea, fecal incontinence, and impaired absorption of fat-soluble vitamins (eg, vitamin D).

(Choice C) Naltrexone is an opioid antagonist indicated for the treatment of opioid abuse and alcohol dependence. It is also used in a combination pill with bupropion for weight loss, in which it is thought to potentiate the otherwise minor weight-loss effects of bupropion.

(Choice D) In addition to treating depression and anxiety, selective serotonin reuptake inhibitors (SSRIs) (eg, fluoxetine) are commonly used in the treatment of eating disorders, especially bulimia nervosa. Although some patients taking SSRIs experience minor weight loss, the effects on weight are variable, and these medications are not prescribed for weight loss.

Educational objective:
Norepinephrine-releasing agents (eg, phentermine) are sympathomimetic weight-loss drugs indicated for short-term treatment of obesity. They stimulate the release and inhibit the reuptake of norepinephrine. Subjective effects include an increased sensation of satiety, leading to reduced caloric intake. Weight regain after cessation is common with these drugs.

https://t.me/USMLEWorldStep1

Norepinephrine-releasing agents (eg, **phentermine**) are sympathomimetic weight-loss drugs indicated for **short-**

term (

and, to

subse

Becau

should

can in

weight

(Choi

and ar

gastric

(Choi

dietary

fecal i

(Choi

depen

the oth

(Choi

fluoxet

patien

not pre

Educa

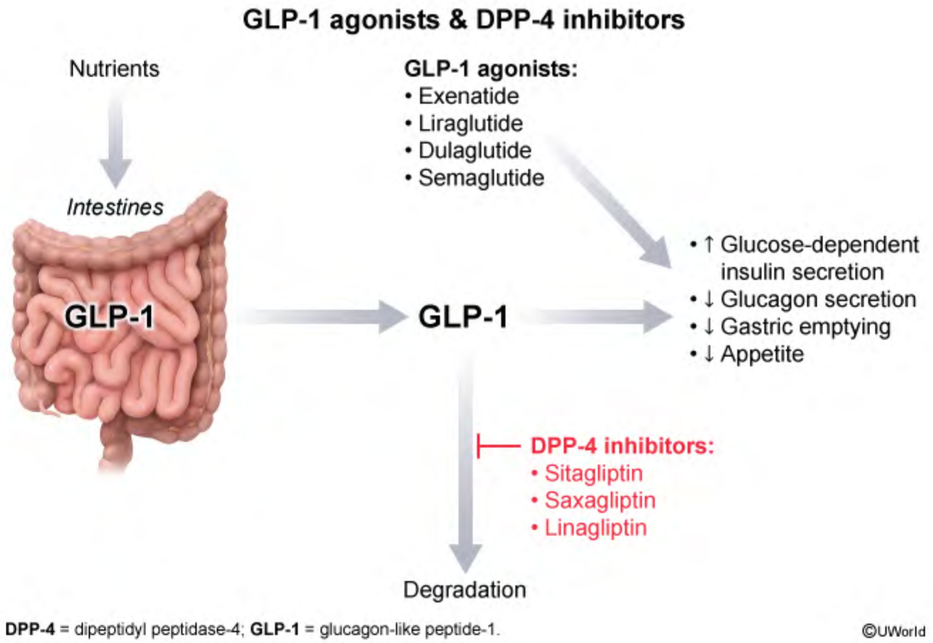
Norep

term tr

effects

common with these drugs.

Exhibit Display



Zoom In Zoom Out Reset New | Existing My Notebook

https://t.me/USMLEWorldStep1

A 58-year-old man is seen in the clinic 6 months after undergoing right coronary artery stent placement due to unstable angina. His father died at age 50 from coronary artery disease. The patient follows a healthy diet and exercise plan and is compliant with his current medication regimen. BMI is 29 kg/m^2. Physical examination is unremarkable. After extensive discussion with the patient, evolocumab is added to his treatment plan. Which of the following is expected as an immediate result of this treatment?

- A. Decreased hepatocyte cholesterol synthesis
- B. Decreased intestinal cholesterol absorption
- C. Decreased low-density lipoprotein receptor lysosomal degradation
- D. Stimulation of lipoprotein lipase transcription
- E. Stimulation of low-density lipoprotein receptor transcription

Submit

https://t.me/USMLEWorldStep1

A 58-year-old man is seen in the clinic 6 months after undergoing right coronary artery stent placement due to unstable angina. His father died at age 50 from coronary artery disease. The patient follows a healthy diet and exercise plan and is compliant with his current medication regimen. BMI is 29 kg/m^2. Physical examination is unremarkable. After extensive discussion with the patient, evolocumab is added to his treatment plan. Which of the following is expected as an immediate result of this treatment?

- A. Decreased hepatocyte cholesterol synthesis (3%)
- ✗ B. Decreased intestinal cholesterol absorption (8%)
- ✓ C. Decreased low-density lipoprotein receptor lysosomal degradation (70%)
- D. Stimulation of lipoprotein lipase transcription (5%)
- E. Stimulation of low-density lipoprotein receptor transcription (12%)

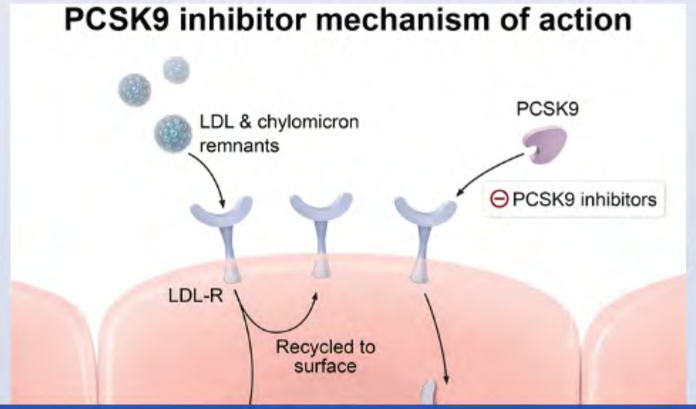
Incorrect
Correct answer
C

70%
Answered correctly

03 secs
Time Spent

2023
Version

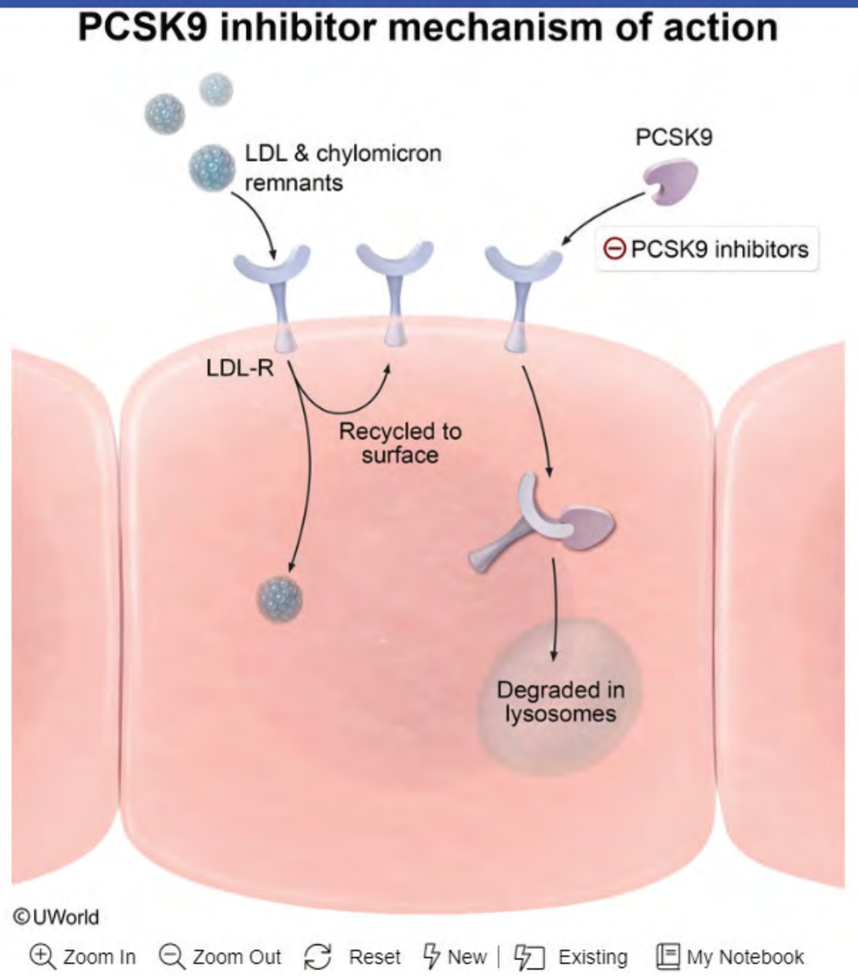
Explanation



https://t.me/USMLEWorldStep1

A 58-year-old man is seen in the clinic 6 months after undergoing right coronary artery stent placement due to unstab
exerci
unrem
the fol

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Inco
Corre
C

Expl

https://t.me/USMLEWorldStep1

Proprotein convertase subtilisin kexin 9 (PCSK9) is a serine protease that regulates the concentration of **low-density lipoprotein receptor** (LDL-R) on the hepatocyte cell surface. Binding of PCSK9 to LDL-R causes increased lysosomal degradation of LDL-R, which leads to decreased uptake of circulating LDL into hepatocytes.

PCSK9 inhibitors (eg, evolocumab, alirocumab) are monoclonal antibodies that inhibit binding of PCSK9 to LDL-R, which **decreases LDL-R degradation** and increases the concentration of LDL-R remaining on the cell surface. This results in **greater uptake of LDL in the liver** and lower circulating LDL levels.

When statins are used to treat high LDL levels, circulating levels of PCSK9 are upregulated, suggesting that PCSK9 pathway inhibition may complement the LDL–lowering effect of statins. Therefore, PCSK9 inhibitors are indicated for high-risk patients who have **persistently elevated LDL** despite statin therapy; PCSK9 inhibitors reduce the risk of cardiovascular events (eg, myocardial infarction, stroke) in these patients.

(Choice A) Statins (eg, atorvastatin) are the primary, first-line lipid-lowering agents for patients who have atherosclerotic cardiovascular disease or are at increased atherosclerotic risk. They decrease hepatic cholesterol synthesis by inhibiting HMG-CoA reductase.

(Choice B) Ezetimibe is a lipid-lowering drug that directly inhibits absorption of cholesterol in the small intestine. PCSK9 inhibitors do not inhibit intestinal cholesterol absorption.

(Choice D) Insulin upregulates lipoprotein lipase, which hydrolyzes triglycerides in chylomicrons and VLDL; the liberated fatty acids are taken up in adipose tissue, leading to reduced plasma triglyceride levels. In contrast, PCSK9 inhibitors have little effect on triglycerides.

(Choice E) Thyroid hormone increases expression of LDL-R, as does estrogen and various dietary factors (eg, low saturated fat diet). However, the increase in cell-surface LDL-R from PCSK9 inhibitors is due to decreased lysosomal degradation, not increased transcription (synthesis).

Educational objective:
Binding of proprotein convertase subtilisin kexin 9 (PCSK9) to low-density lipoprotein receptor (LDL-R) on the hepatocyte cell surface increases degradation of LDL-R, leading to decreased uptake of circulating LDL. PCSK9 inhibitors (eg, evolocumab, alirocumab) decrease LDL-R degradation, resulting in greater uptake of LDL in the liver and lower circulating LDL levels.

https://t.me/USMLEWorldStep1

Proprotein convertase subtilisin kexin 9 (PCSK9) is a serine protease that regulates the concentration of **low-densit**
increa

PCSK
R, whi
This re

When
PCSK
indicat
reduce

(Choi
athero
synthe

(Choi
PCSK

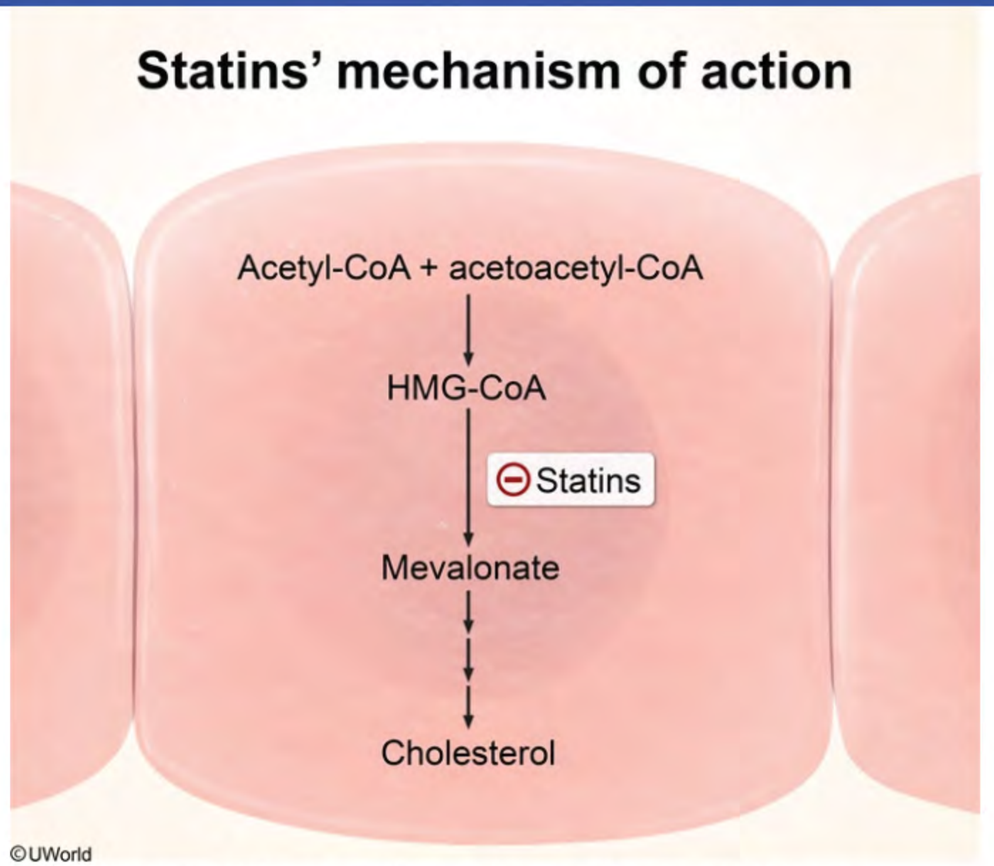
(Choi
liberat
PCSK

(Choi
low sa
lysoso

Educa
Bindin

hepatocyte cell surface increases degradation of LDL-R, leading to decreased uptake of circulating LDL. PCSK9 inhibitors (eg, evolocumab, alirocumab) decrease LDL-R degradation, resulting in greater uptake of LDL in the liver and lower circulating LDL levels.

Exhibit Display



Zoom In Zoom Out Reset New | Existing My Notebook

https://t.me/USMLEWorldStep1

Proprotein convertase subtilisin kexin 9 (PCSK9) is a serine protease that regulates the concentration of **low-**

densit

increa

PCSK

R, whi

This re

When

PCSK

indicat

reduce

(Choi

athero

synthe

(Choi

PCSK

(Choi

liberat

PCSK

(Choi

low sa

lysoso

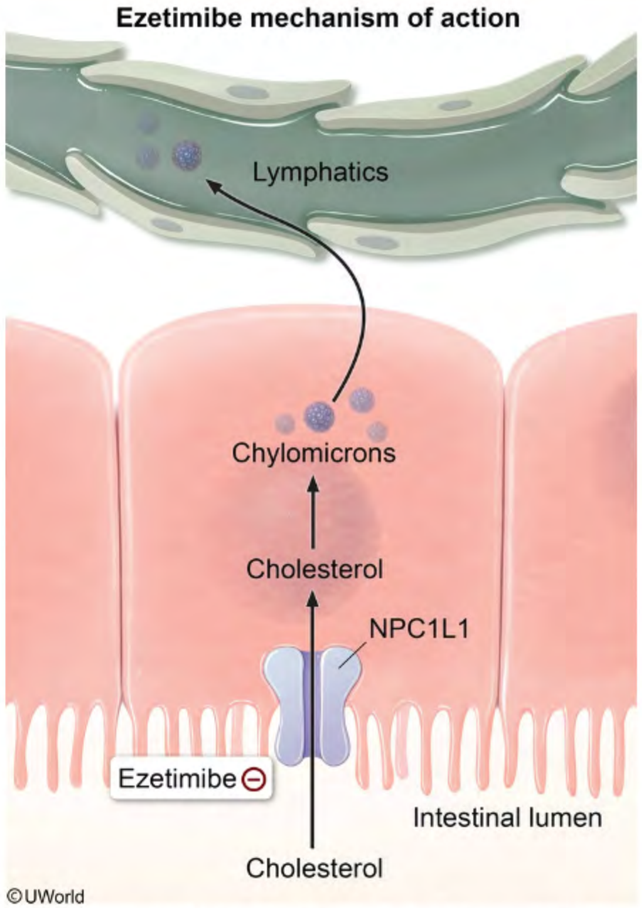
Educa

Bindin

hepato

inhibitors (eg, evolocumab, alirocumab) decrease LDL-R degradation, resulting in greater uptake of LDL in the liver and lower circulating LDL levels.

Exhibit Display



Zoom In Zoom Out Reset New | Existing My Notebook

https://t.me/USMLEWorldStep1

Proprotein convertase subtilisin kexin 9 (PCSK9) is a serine protease that regulates the concentration of **low-**

densit

increa

PCSK

R, whi

This re

When

PCSK

indicat

reduce

(Choi

athero

synthe

(Choi

PCSK

(Choi

liberat

PCSK

(Choi

low sa

lysoso

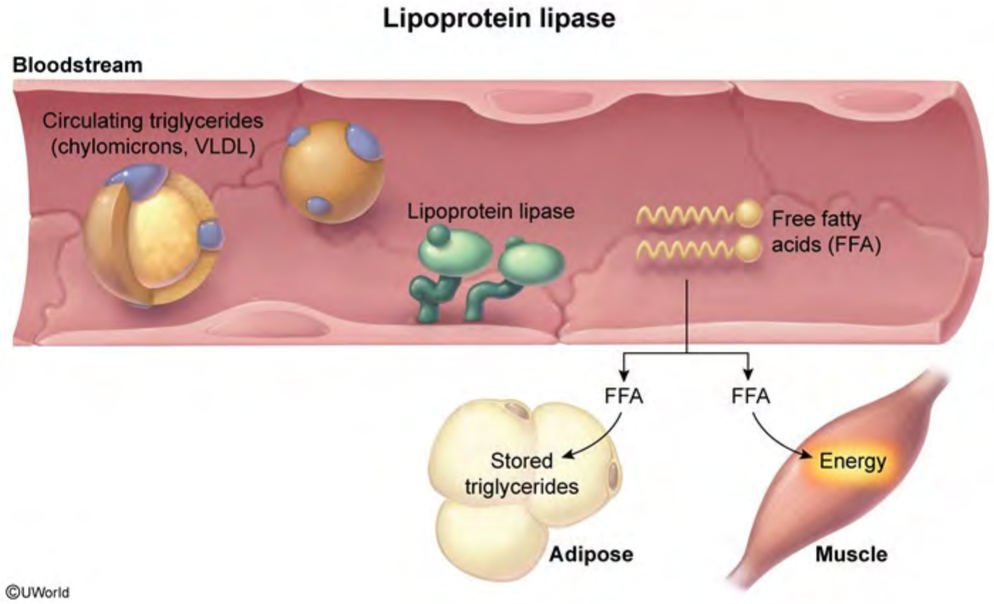
Educa

Bindin

hepato

inhibitors (eg, evolocumab, alirocumab) decrease LDL-R degradation, resulting in greater uptake of LDL in the liver and lower circulating LDL levels.

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

Proprotein convertase subtilisin kexin 9 (PCSK9) is a serine protease that regulates the concentration of **low-densit**
increa

PCSK
R, whi
This re

When
PCSK
indicat
reduce

(Choi
athero
synthe

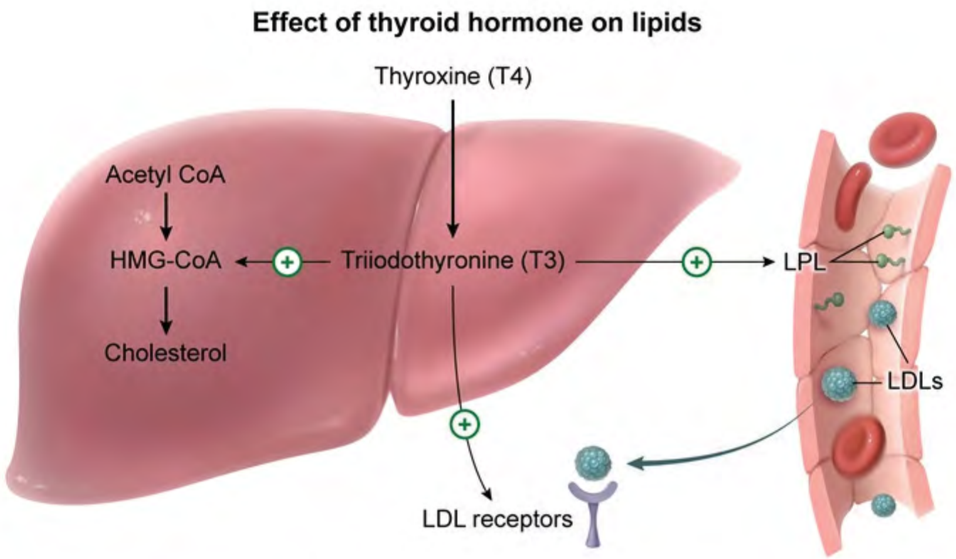
(Choi
PCSK

(Choi
liberat
PCSK

(Choi
low sa
lysoso

Educa
Bindin
hepato
inhibitors (eg, evolocumab, alirocumab) decrease LDL-R degradation, resulting in greater uptake of LDL in the liver and lower circulating LDL levels.

Exhibit Display



LDLs = low-density lipoproteins; **LPL** = lipoprotein lipase.

©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

A 25-year-old woman comes to the office due to a 2-week history of neck pain. The patient had an upper respiratory infection a month ago, during which she experienced nasal congestion, rhinorrhea, and a cough productive of clear sputum; her respiratory symptoms lasted for 5 days and resolved spontaneously. The patient then felt well until 2 weeks ago, when she developed pain in the anterior neck associated with mild fever, palpitations, and excessive sweating. She is otherwise healthy and takes no medications. Pulse is 110/min. The thyroid gland is tender to palpation and diffusely enlarged. Other findings include sweaty palms, fine hand tremor, and brisk deep tendon reflexes. Laboratory studies show suppressed TSH and elevated free thyroxine levels. Erythrocyte sedimentation rate is 70 mm/hr. Which of the following additional findings is most likely to be present in this patient at this time?

- A. Elevated thyroid peroxidase antibody level
- B. Low radioactive iodine uptake
- C. Low serum thyroglobulin
- D. Low serum triiodothyronine level

Submit

https://t.me/USMLEWorldStep1

A 25-year-old woman comes to the office due to a 2-week history of neck pain. The patient had an upper respiratory infection a month ago, during which she experienced nasal congestion, rhinorrhea, and a cough productive of clear sputum; her respiratory symptoms lasted for 5 days and resolved spontaneously. The patient then felt well until 2 weeks ago, when she developed pain in the anterior neck associated with mild fever, palpitations, and excessive sweating. She is otherwise healthy and takes no medications. Pulse is 110/min. The thyroid gland is tender to palpation and diffusely enlarged. Other findings include sweaty palms, fine hand tremor, and brisk deep tendon reflexes. Laboratory studies show suppressed TSH and elevated free thyroxine levels. Erythrocyte sedimentation rate is 70 mm/hr. Which of the following additional findings is most likely to be present in this patient at this time?

- ✗ A. Elevated thyroid peroxidase antibody level (27%)
- ✓ B. Low radioactive iodine uptake (42%)
- C. Low serum thyroglobulin (25%)
- D. Low serum triiodothyronine level (5%)

Incorrect
Correct answer
B

42%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

Subacute thyroiditis	
Pathogenesis	• Postviral inflammatory response • Destruction of thyroid follicles with release of preformed thyroid hormone
Clinical features	• Painful/tender goiter • Fever • Initial hyperthyroid phase → hypothyroid phase → return to euthyroid

https://t.me/USMLEWorldStep1

Explanation

Subacute thyroiditis	
Pathogenesis	• Postviral inflammatory response • Destruction of thyroid follicles with release of preformed thyroid hormone
Clinical features	• Painful/tender goiter • Fever • Initial hyperthyroid phase → hypothyroid phase → return to euthyroid
Diagnostic testing	• Elevated thyroid hormone, suppressed TSH (hyperthyroid phase) • Elevated serum thyroglobulin • Elevated erythrocyte sedimentation rate • Low radioiodine uptake

This patient has **primary hyperthyroidism** (ie, intrinsic thyroid disease), confirmed with elevated free thyroxine and low TSH. Common nonspecific findings in hyperthyroidism include diaphoresis, tachypalpitations, tremor, brisk reflexes, and lid lag. In addition, she has features suggesting **subacute (granulomatous, de Quervain) thyroiditis** (ST), including fever; a painful, tender goiter; and an elevated erythrocyte sedimentation rate (nonspecific marker for inflammation).

ST characteristically follows a **viral infection** and is thought to be due to a cross-reacting inflammatory response with activation of cytotoxic T lymphocytes. Diagnostic findings in ST include:

- elevated thyroid hormone levels (ie, thyroxine [T4], triiodothyronine [T3]) due to the destruction of thyroid follicles and **release of preformed thyroid hormone**.
- **elevated thyroglobulin**, which is released from thyroid follicles with thyroid hormone.
- suppressed TSH due to feedback inhibition by thyroid hormone on the pituitary.
- **low radioactive iodine uptake** (ie, radioiodine thyroid scintigraphy) reflecting decreased thyroid metabolic activity and organification of iodine due to loss of TSH stimulation.

https://t.me/USMLEWorldStep1

Diagnostic testing	• Elevated serum thyroglobulin • Elevated erythrocyte sedimentation rate • Low radioiodine uptake

This patient has **primary hyperthyroidism** (ie, intrinsic thyroid disease), confirmed with elevated free thyroxine and low TSH. Common nonspecific findings in hyperthyroidism include diaphoresis, tachypalpitations, tremor, brisk reflexes, and lid lag. In addition, she has features suggesting **subacute (granulomatous, de Quervain) thyroiditis** (ST), including fever; a painful, tender goiter; and an elevated erythrocyte sedimentation rate (nonspecific marker for inflammation).

ST characteristically follows a **viral infection** and is thought to be due to a cross-reacting inflammatory response with activation of cytotoxic T lymphocytes. Diagnostic findings in ST include:

- elevated thyroid hormone levels (ie, thyroxine [T4], triiodothyronine [T3]) due to the destruction of thyroid follicles and **release of preformed thyroid hormone**.
- **elevated thyroglobulin**, which is released from thyroid follicles with thyroid hormone.
- suppressed TSH due to feedback inhibition by thyroid hormone on the pituitary.
- **low radioactive iodine uptake** (ie, radioiodine thyroid scintigraphy) reflecting decreased thyroid metabolic activity and organification of iodine due to loss of TSH stimulation.
- diffuse enlargement of the gland with **decreased blood flow** on thyroid ultrasound.

Following the hyperthyroid phase, patients experience transient hypothyroidism due to depletion of thyroid colloid and then slowly return to a euthyroid state.

(Choice A) Thyroid peroxidase antibodies are a marker for autoimmune thyroid disorders, including postpartum and chronic lymphocytic (Hashimoto) thyroiditis and Graves disease. Goiter is common in these conditions but is painless and nontender.

(Choice C) Exogenous thyroid hormone intake (eg, levothyroxine, porcine thyroid extract) can cause hyperthyroidism with suppression of TSH and decreased endogenous release of thyroid hormone and thyroglobulin. However, the native thyroid is not enlarged and is often atrophic.

https://t.me/USMLEWorldStep1

with activation of cytotoxic T lymphocytes. Diagnostic findings in ST include:

- elevated thyroid hormone levels (ie, thyroxine [T4], triiodothyronine [T3]) due to the destruction of thyroid follicles and **release of preformed thyroid hormone**.
- **elevated thyroglobulin**, which is released from thyroid follicles with thyroid hormone.
- suppressed TSH due to feedback inhibition by thyroid hormone on the pituitary.
- **low radioactive iodine uptake** (ie, radioiodine thyroid scintigraphy) reflecting decreased thyroid metabolic activity and organification of iodine due to loss of TSH stimulation.
- diffuse enlargement of the gland with **decreased blood flow** on thyroid ultrasound.

Following the hyperthyroid phase, patients experience transient hypothyroidism due to depletion of thyroid colloid and then slowly return to a euthyroid state.

(Choice A) Thyroid peroxidase antibodies are a marker for autoimmune thyroid disorders, including postpartum and chronic lymphocytic (Hashimoto) thyroiditis and Graves disease. Goiter is common in these conditions but is painless and nontender.

(Choice C) Exogenous thyroid hormone intake (eg, levothyroxine, porcine thyroid extract) can cause hyperthyroidism with suppression of TSH and decreased endogenous release of thyroid hormone and thyroglobulin. However, the native thyroid is not enlarged and is often atrophic.

(Choice D) Euthyroid sick syndrome (low T3 syndrome) is a characteristic set of thyroid function abnormalities in patients with severe systemic illness. It resembles mild, central hypothyroidism with normal/low TSH and low T3 levels. The thyroid is not enlarged or tender, and the syndrome is not usually seen following ordinary upper respiratory illnesses.

Educational objective:
Subacute (granulomatous, de Quervain) thyroiditis presents with fever; a painful, tender goiter; and an elevated erythrocyte sedimentation rate. Patients initially develop hyperthyroidism due to the destruction of thyroid follicles and release of preformed thyroid hormone. TSH is suppressed due to feedback inhibition on the pituitary; as a result, thyroid metabolic activity and organification of iodine are decreased, and radioactive iodine uptake is low.

https://t.me/USMLEWorldStep1

A 13-year-old boy is evaluated for abnormal growth. His mother says that he has grown rapidly over the past 10 months and is much taller than his older brother and other children his age. During this time, she has had a hard time finding clothes that fit him and has had to buy new shoes for him each month due to increasing foot size. The patient says that he feels well except for excessive sweating. He has no history of major medical illness and takes no medications. Both parents are of average height and have normally proportioned limbs. The patient is above the 99th percentile for height and at the 90th percentile for weight. On physical examination, he has long extremities with large hands and feet; the lower jaw is protruding. Heart sounds are normal. Sexual development is Tanner stage 4. Which of the following is the most likely underlying cause of this patient's condition?

- A. Aneuploidy of the X chromosome
- B. De novo mutation in the fibrillin-1 gene
- C. Defective growth hormone receptor
- D. Excessive liver production of IGF-1
- E. Excessive thyroxine production
- F. Increased hypothalamic release of IGF-1
- G. Increased pituitary gonadotropin release

Submit

https://t.me/USMLEWorldStep1

A 13-year-old boy is evaluated for abnormal growth. His mother says that he has grown rapidly over the past 10 months and is much taller than his older brother and other children his age. During this time, she has had a hard time finding clothes that fit him and has had to buy new shoes for him each month due to increasing foot size. The patient says that he feels well except for excessive sweating. He has no history of major medical illness and takes no medications. Both parents are of average height and have normally proportioned limbs. The patient is above the 99th percentile for height and at the 90th percentile for weight. On physical examination, he has long extremities with large hands and feet; the lower jaw is protruding. Heart sounds are normal. Sexual development is Tanner stage 4. Which of the following is the most likely underlying cause of this patient's condition?

- A. Aneuploidy of the X chromosome (3%)
- ✗ B. De novo mutation in the fibrillin-1 gene (5%)
- C. Defective growth hormone receptor (5%)
- ✓ D. Excessive liver production of IGF-1 (58%)
- E. Excessive thyroxine production (1%)
- F. Increased hypothalamic release of IGF-1 (13%)
- G. Increased pituitary gonadotropin release (11%)

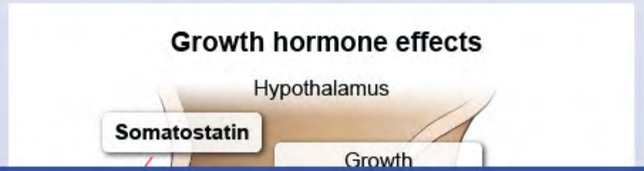
Incorrect
Correct answer
D

58%
Answered correctly

03 secs
Time Spent

2023
Version

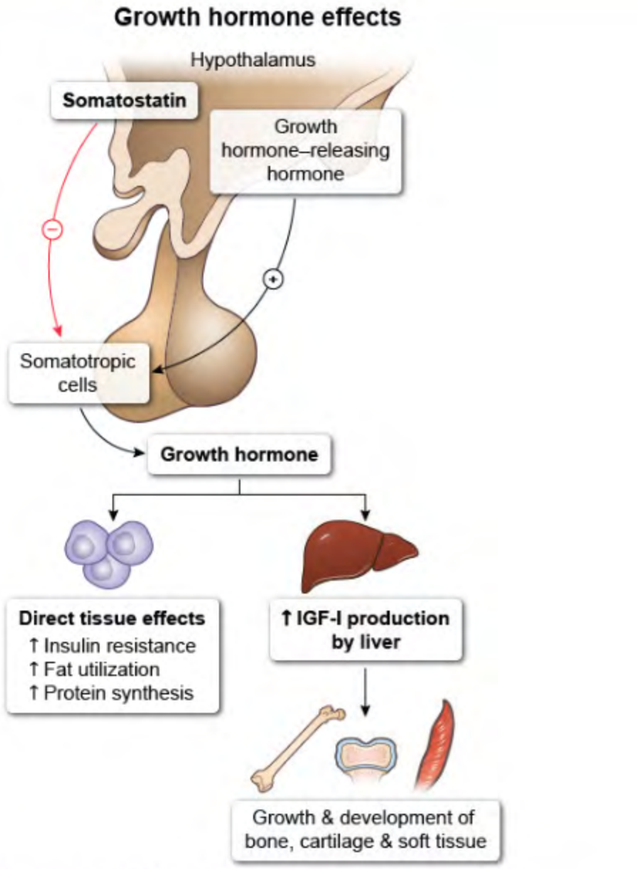
Explanation



https://t.me/USMLEWorldStep1

G. Increased pituitary gonadotropin release (11%)

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

bone, cartilage & soft tissue

IGF-1 = insulin-like growth factor-1. ©UWorld

This patient most likely has **gigantism**, a condition caused by hypersecretion of **growth hormone (GH)** during childhood. GH is a peptide hormone secreted by the anterior pituitary that acts as both a growth promoter and stress hormone (increasing glucose and free fatty acid levels). Although GH has direct effects on target tissue (eg, chondrogenesis, myocyte protein synthesis), its growth-promoting effects are primarily mediated by **insulin-like growth factor-1 (IGF-1)**, which is released from the liver following stimulation of hepatic GH receptors. IGF-1 binds to a specific receptor tyrosine kinase and stimulates cell growth and proliferation in bone, cartilage, skeletal muscle, and other soft tissues.

Gigantism occurs in children and adolescents before fusion of the epiphyseal growth plates, resulting in **rapid linear growth** along with large hands and feet, thickening of the calvarium, protrusion of the jaw (**prognathism**), excessive sweating, and oily skin. The adult variant, acromegaly, has no effect on stature because the epiphyseal growth plates have already fused.

(Choices A and B) Klinefelter syndrome is caused by a nondisjunction of sex chromosomes (47,XXY). Patients are phenotypically male with hypogonadism and infertility. Marfan syndrome is caused by a defect in fibrillin-1 and presents with joint hypermobility, increased limb length, and arachnodactyly. These disorders are associated with tall stature but do not exhibit prognathism or bony enlargement of the hands and feet.

(Choice C) Defects in the GH receptor cause Laron dwarfism, characterized by decreased linear growth, high serum GH concentrations, and low levels of circulating IGF-1.

(Choice E) Excessive thyroxine production (ie, hyperthyroidism) presents with weight loss, heat intolerance, and tremor. Sweating is common, but hyperthyroidism in children causes short stature, not accelerated growth.

(Choice F) Circulating levels of IGF-1 are produced primarily in the liver. Although IGF-1 is also produced locally in the hypothalamus to regulate central nervous system activity, this source does not contribute significantly to bone and soft-tissue growth.

(Choice G) Increased pituitary gonadotropin release causes central precocious puberty. This patient has appropriate sexual development for age.

Educational objective:

https://t.me/USMLEWorldStep1

binds to a specific receptor tyrosine kinase and stimulates cell growth and proliferation in bone, cartilage, skeletal muscle, and other soft tissues.

Gigantism occurs in children and adolescents before fusion of the epiphyseal growth plates, resulting in **rapid linear growth** along with large hands and feet, thickening of the calvarium, protrusion of the jaw (**prognathism**), excessive sweating, and oily skin. The adult variant, acromegaly, has no effect on stature because the epiphyseal growth plates have already fused.

(Choices A and B) Klinefelter syndrome is caused by a nondisjunction of sex chromosomes (47,XXY). Patients are phenotypically male with hypogonadism and infertility. Marfan syndrome is caused by a defect in fibrillin-1 and presents with joint hypermobility, increased limb length, and arachnodactyly. These disorders are associated with tall stature but do not exhibit prognathism or bony enlargement of the hands and feet.

(Choice C) Defects in the GH receptor cause Laron dwarfism, characterized by decreased linear growth, high serum GH concentrations, and low levels of circulating IGF-1.

(Choice E) Excessive thyroxine production (ie, hyperthyroidism) presents with weight loss, heat intolerance, and tremor. Sweating is common, but hyperthyroidism in children causes short stature, not accelerated growth.

(Choice F) Circulating levels of IGF-1 are produced primarily in the liver. Although IGF-1 is also produced locally in the hypothalamus to regulate central nervous system activity, this source does not contribute significantly to bone and soft-tissue growth.

(Choice G) Increased pituitary gonadotropin release causes central precocious puberty. This patient has appropriate sexual development for age.

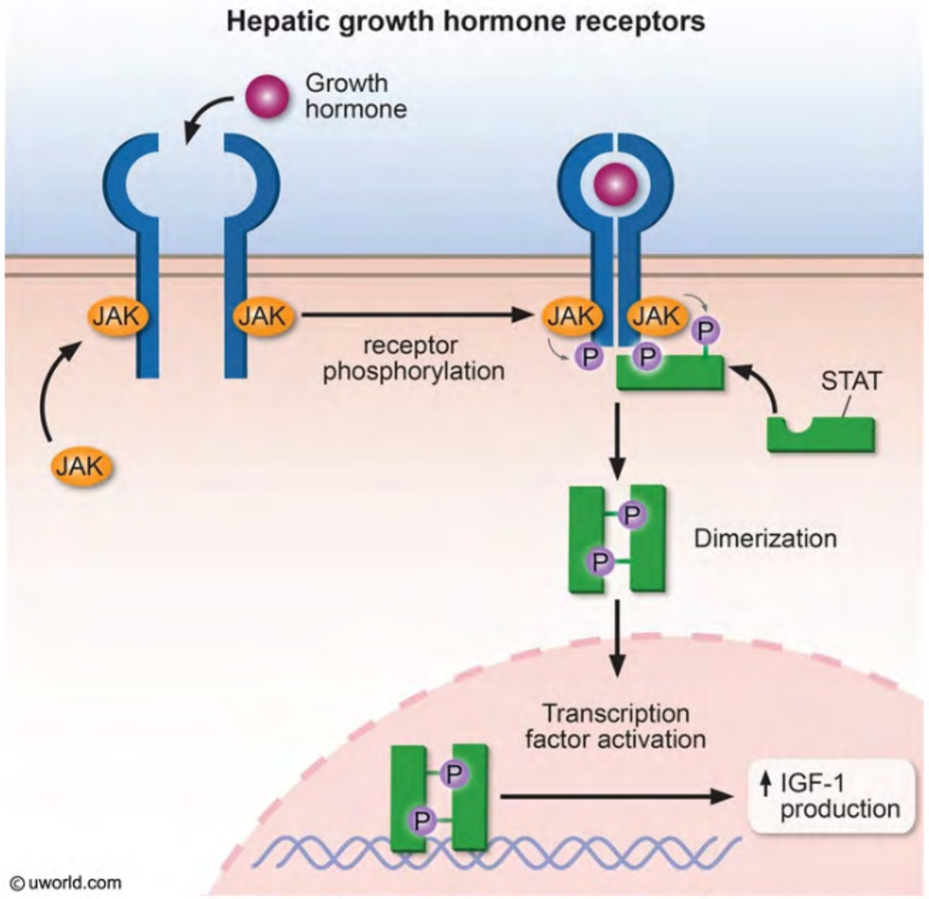
Educational objective:
Gigantism is caused by excess growth hormone (GH) during childhood and is characterized by accelerated linear growth, prognathism, and bony enlargement of the hands and feet. GH excess after closure of the epiphysial growth plates causes acromegaly. GH has direct effects on target tissues and indirect effects mediated by insulin-like growth factor-1 secretion from the liver.

References

- Pituitary gigantism: causes and clinical characteristics.

https://t.me/USMLEWorldStep1

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

This p
childh
stress
chond
growt
binds
muscl

Gigant
linear
excess
growth

(Choi
are ph
preser
tall sta

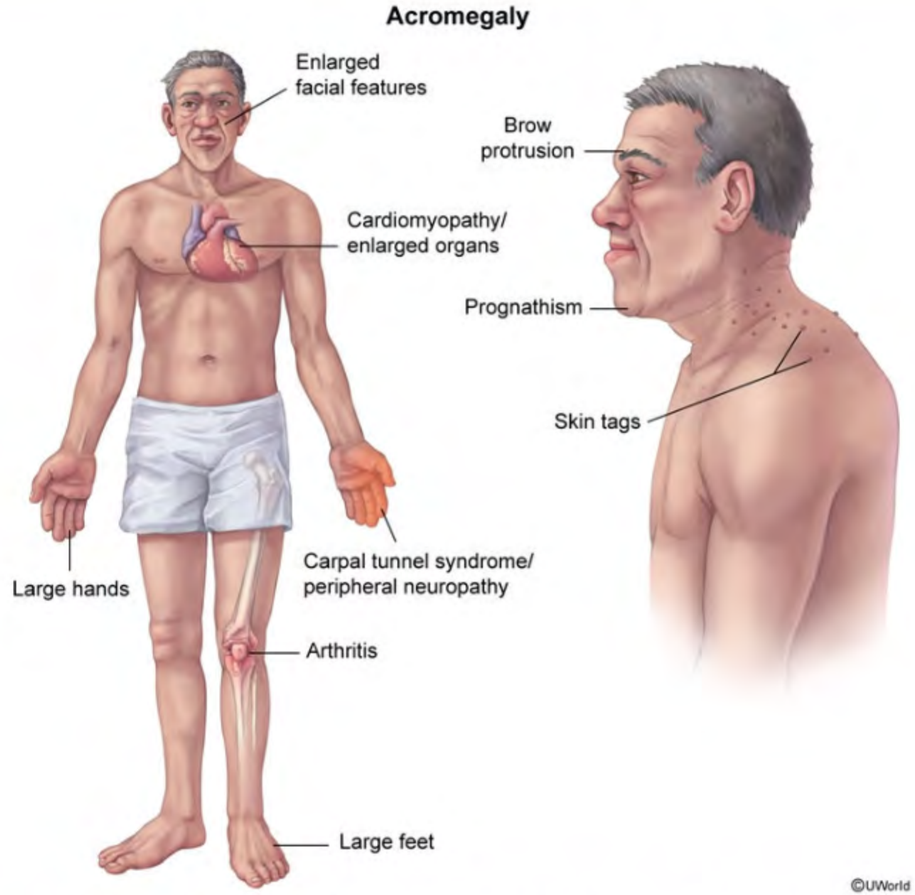
(Choi
serum

(Choi
tremor

(Choi
in the hypothalamus to regulate central nervous system activity, this source does not contribute significantly to bone and soft-tissue growth.

https://t.me/USMLEWorldStep1

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

This p
childh
stress
chond
growt
binds
muscl

Gigant
linear
excess
growth

(Choi
are ph
preser
tall sta

(Choi
serum

(Choi
tremor

(Choi
in the hypothalamus to regulate central nervous system activity, this source does not contribute significantly to bone and soft-tissue growth.

https://t.me/USMLEWorldStep1

A 45-year-old woman comes to the office due to a 4-month history of headaches and blurred vision. She takes no medications and has no other medical conditions. After the initial laboratory work-up, a CT scan of the abdomen is performed that reveals a 2-cm left-sided adrenal mass. The patient undergoes an uncomplicated left-sided adrenalectomy. Gross examination of the adrenal gland demonstrates a well-defined yellowish tumor within the cortex. Further evaluation reveals that the tumor cells are functionally similar to cells from the outermost hormone-producing layer of the adrenal cortex. This patient would most likely have had which of the following additional symptoms?

- A. Diarrhea and flushing
- B. Excessive hair growth
- C. Paresthesia and muscle weakness
- D. Sweating and tremulousness
- E. Weight gain and easy bruising

Submit

https://t.me/USMLEWorldStep1

A 45-year-old woman comes to the office due to a 4-month history of headaches and blurred vision. She takes no medications and has no other medical conditions. After the initial laboratory work-up, a CT scan of the abdomen is performed that reveals a 2-cm left-sided adrenal mass. The patient undergoes an uncomplicated left-sided adrenalectomy. Gross examination of the adrenal gland demonstrates a well-defined yellowish tumor within the cortex. Further evaluation reveals that the tumor cells are functionally similar to cells from the outermost hormone-producing layer of the adrenal cortex. This patient would most likely have had which of the following additional symptoms?

- A. Diarrhea and flushing
- ✗ B. Excessive hair growth
- ✓ C. Paresthesia and muscle weakness
- D. Sweating and tremulousness
- E. Weight gain and easy bruising

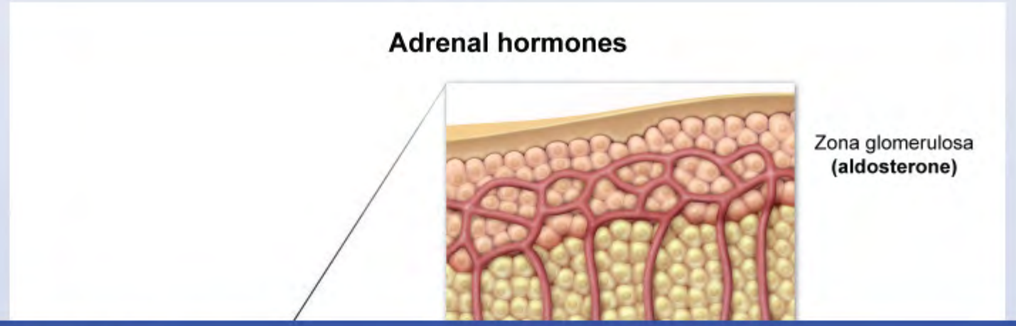
Incorrect
Correct answer
C

Collecting Statistics

36 secs
Time Spent

2023
Version

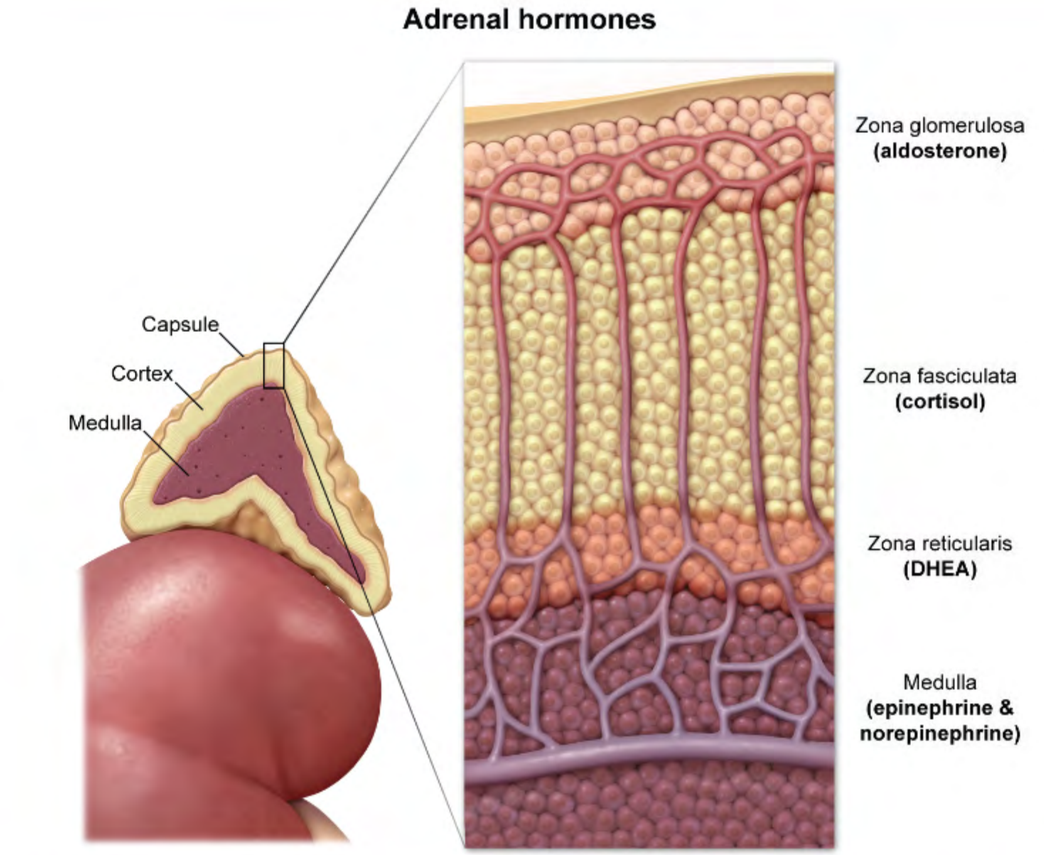
Explanation



https://t.me/USMLEWorldStep1

A 45-year-old woman comes to the office due to a 4-month history of headaches and blurred vision. She takes no
medic
perfor
adrena
cortex
produc
sympt

Exhibit Display



Zoom In Zoom Out Reset New | Existing My Notebook

https://t.me/USMLEWorldStep1

This patient with headaches and blurred vision (suggestive of severe hypertension) underwent resection of an **adrenocortical adenoma** (well-defined, yellowish tumor). Hyperfunctioning adrenocortical adenomas secrete hormones depending on the location of the cells within the adrenal cortex. In this patient, the tumor cells arise from the **outermost layer** (zona glomerulosa), which is responsible for producing **aldosterone**.

Hypersecretion of aldosterone by an adrenocortical adenoma is a common cause of primary hyperaldosteronism (Conn syndrome). Aldosterone, which is normally regulated by angiotensin II and potassium (K^+) levels, stimulates reabsorption of sodium (Na^+) and secretion of K^+ and hydrogen (H^+) in the renal collecting ducts. Excess aldosterone therefore causes increased intravascular volume and **hypertension**, in addition to predisposing to metabolic alkalosis and **hypokalemia**. Hypokalemia can cause muscle cramps, **muscle weakness**, and **paresthesia** due to hyperpolarization, which impairs membrane depolarization.

Despite increased Na^+ reabsorption, extravascular volume overload (weight gain, peripheral edema) rarely occurs due to aldosterone escape. With aldosterone escape, increased intravascular volume increases pressure natriuresis and augments atrial natriuretic peptide release, thereby limiting net Na^+ retention and extravascular fluid accumulation.

(Choice A) Diarrhea and flushing may be seen in carcinoid syndrome, a rare condition most often caused by a serotonin (5-HT)-secreting tumor derived from neuroendocrine cells of the gastrointestinal tract.

(Choice B) Excessive hair growth (hirsutism) can result from excess androgen production. An adrenal tumor causing androgen hypersecretion would have the functionality of the innermost layer of the adrenal cortex (zona reticularis) rather than the outermost layer as in this patient.

(Choice D) Sweating and tremulousness can be caused by excess circulating catecholamines such as from a pheochromocytoma, which can also cause headaches and blurred vision as in this patient. However, these tumors arise from the adrenal *medulla* rather than the adrenal cortex.

(Choice E) Patients with Cushing syndrome often develop weight gain (due to central fat accumulation) and have easy bruising (due to thinning of subcutaneous connective tissue). Cortisol-secreting adrenal tumors would be functionally similar to the middle layer of the adrenal cortex (zona fasciculata).

Educational objective:

https://t.me/USMLEWorldStep1

from the **outermost layer** (zona glomerulosa), which is responsible for producing **aldosterone**.

Hypersecretion of aldosterone by an adrenocortical adenoma is a common cause of primary hyperaldosteronism (Conn syndrome). Aldosterone, which is normally regulated by angiotensin II and potassium (K^+) levels, stimulates reabsorption of sodium (Na^+) and secretion of K^+ and hydrogen (H^+) in the renal collecting ducts. Excess aldosterone therefore causes increased intravascular volume and **hypertension**, in addition to predisposing to metabolic alkalosis and **hypokalemia**. Hypokalemia can cause muscle cramps, **muscle weakness**, and **paresthesia** due to hyperpolarization, which impairs membrane depolarization.

Despite increased Na^+ reabsorption, extravascular volume overload (weight gain, peripheral edema) rarely occurs due to aldosterone escape. With aldosterone escape, increased intravascular volume increases pressure natriuresis and augments atrial natriuretic peptide release, thereby limiting net Na^+ retention and extravascular fluid accumulation.

(Choice A) Diarrhea and flushing may be seen in carcinoid syndrome, a rare condition most often caused by a serotonin (5-HT)-secreting tumor derived from neuroendocrine cells of the gastrointestinal tract.

(Choice B) Excessive hair growth (hirsutism) can result from excess androgen production. An adrenal tumor causing androgen hypersecretion would have the functionality of the innermost layer of the adrenal cortex (zona reticularis) rather than the outermost layer as in this patient.

(Choice D) Sweating and tremulousness can be caused by excess circulating catecholamines such as from a pheochromocytoma, which can also cause headaches and blurred vision as in this patient. However, these tumors arise from the adrenal *medulla* rather than the adrenal cortex.

(Choice E) Patients with Cushing syndrome often develop weight gain (due to central fat accumulation) and have easy bruising (due to thinning of subcutaneous connective tissue). Cortisol-secreting adrenal tumors would be functionally similar to the middle layer of the adrenal cortex (zona fasciculata).

Educational objective:
Hypersecreting adrenocortical tumors can have functionality resembling the outer (aldosterone), middle (cortisol), or inner (androgens) layers of the adrenal cortex. Primary hyperaldosteronism results in hypertension in addition to hypokalemia, which can cause muscle cramps, muscle weakness, and paresthesia.

https://t.me/USMLEWorldStep1



Exhibit Display

Primary hyperaldosteronism	
Etiology	• Bilateral adrenal hyperplasia (60%) • Unilateral adrenal adenoma
Clinical features	• Hypertension • Hypokalemic alkalosis: muscle weakness & paresthesia
Diagnosis	• Elevated plasma aldosterone • Low plasma renin activity • Aldosterone remains elevated following oral saline load

New | Existing | My Notebook

This p
adren
hormo
from th

Hyper
(Conn
reabso
aldost
metab
parest

Despit
due to
natriur
accum

(Choi
seroto

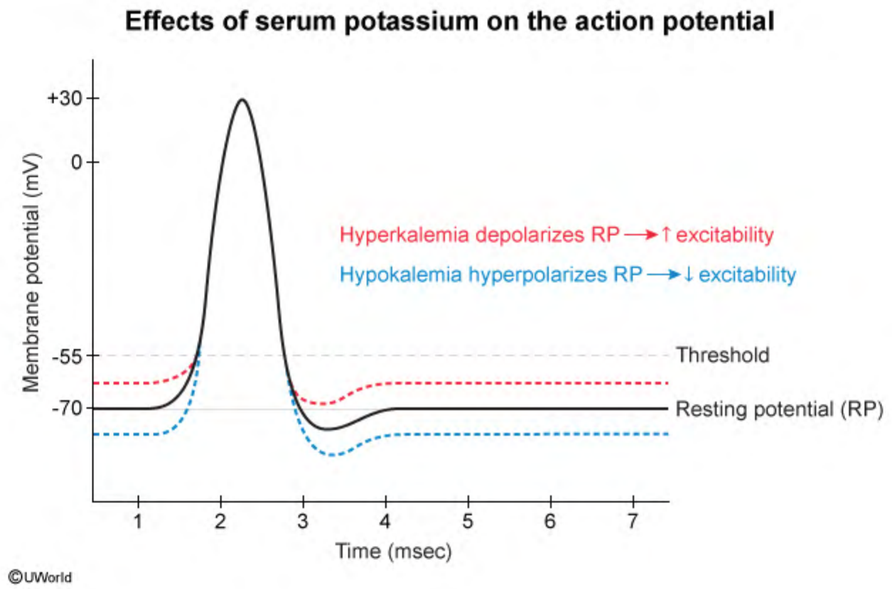
(Choi
causin
reticul

(Choi
pheoc
arise f

(Choice E) Patients with Cushing syndrome often develop weight gain (due to central fat accumulation) and have

https://t.me/USMLEWorldStep1

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

This p
adren
hormo
from th

Hyper
(Conn
reabso
aldost
metab
parest

Despit
due to
natriur
accum

(Choi
seroto

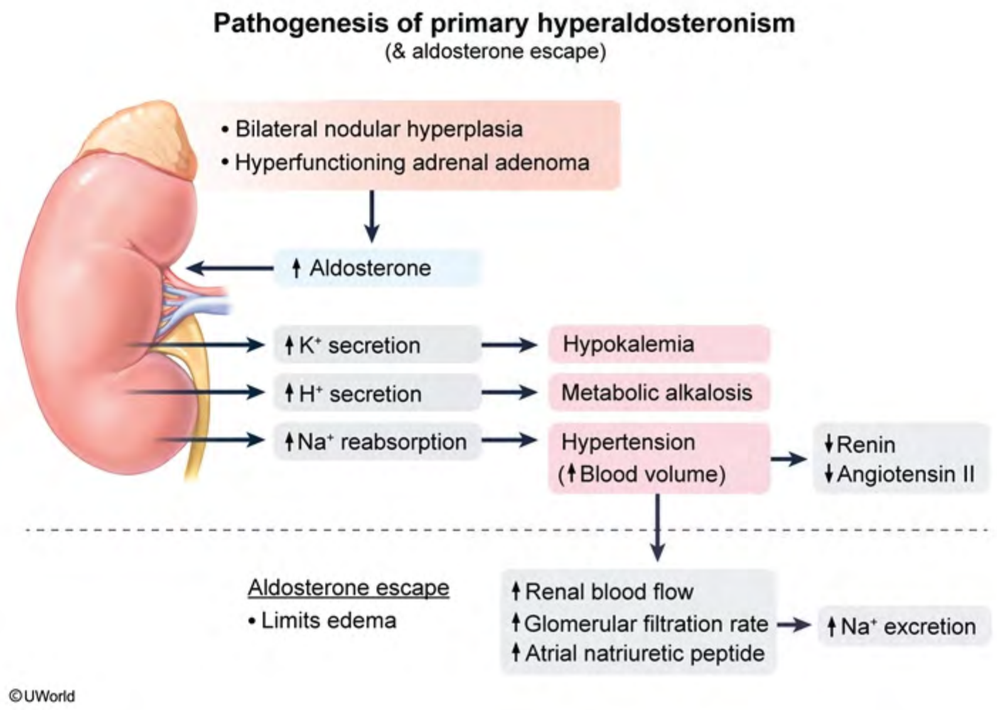
(Choi
causin
reticul

(Choi
pheoc
arise f

(Choice E) Patients with Cushing syndrome often develop weight gain (due to central fat accumulation) and have

https://t.me/USMLEWorldStep1

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

This p
adren
hormo
from th

Hyper
(Conn
reabso
aldoste
metab
parest

Despit
due to
natriur
accum

(Choi
seroto

(Choi
causin
reticul

(Choi
pheoc
arise f

(Choice E) Patients with Cushing syndrome often develop weight gain (due to central fat accumulation) and have

https://t.me/USMLEWorldStep1

A 47-year-old woman comes to the office for follow up of chronic asthma. The patient was recently hospitalized for an asthma exacerbation and required a prolonged period of mechanical ventilation as well as nebulized bronchodilators and intravenous glucocorticoids. Her symptoms improved, and she was discharged on oral prednisone. The patient reports compliance with therapy. She has no other medical conditions and takes no other medications. Blood pressure is 128/72 mm Hg, pulse is 85/min, and respirations are 18/min. On physical examination, there is mild expiratory wheezing. Because of the persistent respiratory findings, the patient is continued on the same treatment regimen. Long-term administration of this oral therapy is most likely to increase which of the following in this patient?

- A. Adrenocortical cell number
- B. Dermal collagen synthesis
- C. Expression of liver enzymes
- D. Lymphoid cell formation
- E. Muscle protein synthesis
- F. Osteoblastic bone formation

Submit

https://t.me/USMLEWorldStep1

A 47-year-old woman comes to the office for follow up of chronic asthma. The patient was recently hospitalized for an asthma exacerbation and required a prolonged period of mechanical ventilation as well as nebulized bronchodilators and intravenous glucocorticoids. Her symptoms improved, and she was discharged on oral prednisone. The patient reports compliance with therapy. She has no other medical conditions and takes no other medications. Blood pressure is 128/72 mm Hg, pulse is 85/min, and respirations are 18/min. On physical examination, there is mild expiratory wheezing. Because of the persistent respiratory findings, the patient is continued on the same treatment regimen. Long-term administration of this oral therapy is most likely to increase which of the following in this patient?

- ✗ A. Adrenocortical cell number (15%)
- B. Dermal collagen synthesis (13%)
- ✓ C. Expression of liver enzymes (46%)
- D. Lymphoid cell formation (7%)
- E. Muscle protein synthesis (8%)
- F. Osteoblastic bone formation (9%)

Incorrect
Correct answer
C

46%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

Effects of prolonged glucocorticoid therapy	
Adipose	• Lipolysis • Altered fat distribution
Adrenal cortex	• Atrophy

https://t.me/USMLEWorldStep1

Effects of prolonged glucocorticoid therapy	
Adipose	• Lipolysis • Altered fat distribution
Adrenal cortex	• Atrophy
Bone	• Osteoporosis
Immune system	• Suppression • T-cell apoptosis
Liver	• Increased gluconeogenesis & glycogenesis
Skeletal muscle	• Atrophy (glucocorticoid myopathy)
Skin	• Thinning • Stria • Impaired wound healing

Glucocorticoids (eg, prednisone) are potent stimulators of liver **gluconeogenesis** and upregulate the synthesis of key gluconeogenic enzymes (eg, phosphoenolpyruvate carboxykinase, glucose-6-phosphatase). Glucocorticoids also increase hepatic glycogen reserves by increasing expression of glycogen synthase, thereby improving glucose availability during periods of acute stress. The increased demand for metabolic enzymes required for these actions leads to an overall **increase in liver protein** synthesis.

Peripherally, glucocorticoids antagonize the actions of insulin in skeletal muscle, favoring **catabolism** and proteolysis to provide substrates for gluconeogenesis and glycogenesis in the liver **(Choice E)**. This effect can manifest as proximal muscle weakness (glucocorticoid myopathy). The effect on adipose tissue is mixed, with lipolytic and antilipolytic effects, altered fat distribution (eg, central obesity, hypertrophy of the dorsocervical fat pad), and increased appetite and caloric intake. The net effect of increased gluconeogenesis and insulin antagonism is **hyperglycemia**.

(Choice A) Long-term glucocorticoid therapy causes atrophy of the adrenal cortex. On abrupt cessation, the

https://t.me/USMLEWorldStep1

Glucocorticoids (eg, prednisone) are potent stimulators of liver **gluconeogenesis** and upregulate the synthesis of key gluconeogenic enzymes (eg, phosphoenolpyruvate carboxykinase, glucose-6-phosphatase). Glucocorticoids also increase hepatic glycogen reserves by increasing expression of glycogen synthase, thereby improving glucose availability during periods of acute stress. The increased demand for metabolic enzymes required for these actions leads to an overall **increase in liver protein** synthesis.

Peripherally, glucocorticoids antagonize the actions of insulin in skeletal muscle, favoring **catabolism** and proteolysis to provide substrates for gluconeogenesis and glycogenesis in the liver **(Choice E)**. This effect can manifest as proximal muscle weakness (glucocorticoid myopathy). The effect on adipose tissue is mixed, with lipolytic and antilipolytic effects, altered fat distribution (eg, central obesity, hypertrophy of the dorsocervical fat pad), and increased appetite and caloric intake. The net effect of increased gluconeogenesis and insulin antagonism is **hyperglycemia**.

(Choice A) Long-term glucocorticoid therapy causes atrophy of the adrenal cortex. On abrupt cessation, the delay in resumption of endogenous cortisol production can precipitate acute adrenal insufficiency.

(Choice B) Glucocorticoids inhibit fibroblast proliferation and collagen formation in the skin. This results in thinning of the skin, impaired wound healing, and stria. The connective tissue that supports the capillaries is also thinned, leading to easy bruising.

(Choice D) Glucocorticoids are potent immunosuppressive agents. They increase expression of anti-inflammatory proteins but decrease expression of inflammatory proteins and cytokines. They also induce apoptosis in T cells (transient lymphopenia is common); circulating neutrophil counts may increase in acute glucocorticoid administration due to increased release from bone marrow and demargination from peripheral tissues.

(Choice F) Glucocorticoids decrease bone mass by multiple mechanisms, including decreased gastrointestinal calcium absorption, increased renal calcium excretion, and direct inhibition of osteoblast activity.

Educational objective:
Glucocorticoids are predominantly catabolic, causing muscle weakness, skin thinning, impaired wound healing, osteoporosis, and immunosuppression. However, they also cause increased hepatic synthesis of gluconeogenic and glycogenic proteins to increase glucose availability. This, along with peripheral antagonism of insulin, contributes to the development of hyperglycemia.

https://t.me/USMLEWorldStep1

improving glucose availability during periods of acute stress. The increased demand for metabolic enzymes required for these actions leads to an overall **increase in liver protein** synthesis.

Peripherally, glucocorticoids antagonize the actions of insulin in skeletal muscle, favoring **catabolism** and proteolysis to provide substrates for gluconeogenesis and glycogenesis in the liver **(Choice E)**. This effect can manifest as proximal muscle weakness (glucocorticoid myopathy). The effect on adipose tissue is mixed, with lipolytic and antilipolytic effects, altered fat distribution (eg, central obesity, hypertrophy of the dorsocervical fat pad), and increased appetite and caloric intake. The net effect of increased gluconeogenesis and insulin antagonism is **hyperglycemia**.

(Choice A) Long-term glucocorticoid therapy causes atrophy of the adrenal cortex. On abrupt cessation, the delay in resumption of endogenous cortisol production can precipitate acute adrenal insufficiency.

(Choice B) Glucocorticoids inhibit fibroblast proliferation and collagen formation in the skin. This results in thinning of the skin, impaired wound healing, and stria. The connective tissue that supports the capillaries is also thinned, leading to easy bruising.

(Choice D) Glucocorticoids are potent immunosuppressive agents. They increase expression of anti-inflammatory proteins but decrease expression of inflammatory proteins and cytokines. They also induce apoptosis in T cells (transient lymphopenia is common); circulating neutrophil counts may increase in acute glucocorticoid administration due to increased release from bone marrow and demargination from peripheral tissues.

(Choice F) Glucocorticoids decrease bone mass by multiple mechanisms, including decreased gastrointestinal calcium absorption, increased renal calcium excretion, and direct inhibition of osteoblast activity.

Educational objective:
Glucocorticoids are predominantly catabolic, causing muscle weakness, skin thinning, impaired wound healing, osteoporosis, and immunosuppression. However, they also cause increased hepatic synthesis of gluconeogenic and glycogenic proteins to increase glucose availability. This, along with peripheral antagonism of insulin, contributes to the development of hyperglycemia.

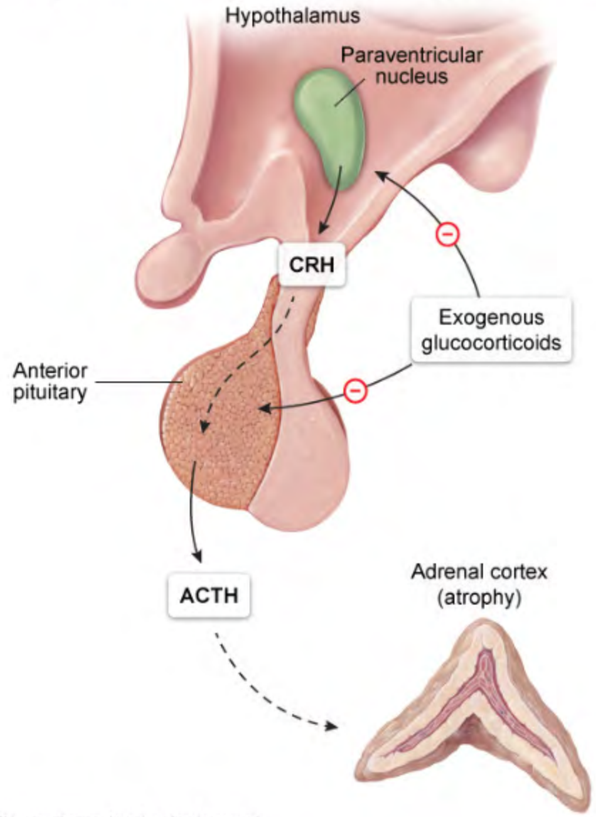
Pharmacology	Endocrine, Diabetes & Metabolism	Corticosteroids
Subject	System	Topic

https://t.me/USMLEWorldStep1

Glucocorticoids (eg, prednisone) are potent stimulators of liver **gluconeogenesis** and upregulate the synthesis of key

Exhibit Display

Suppression of hypothalamic-pituitary-adrenal axis



CRH = corticotropin-releasing hormone.

©UWorld

Zoom In Zoom Out Reset New | Existing My Notebook

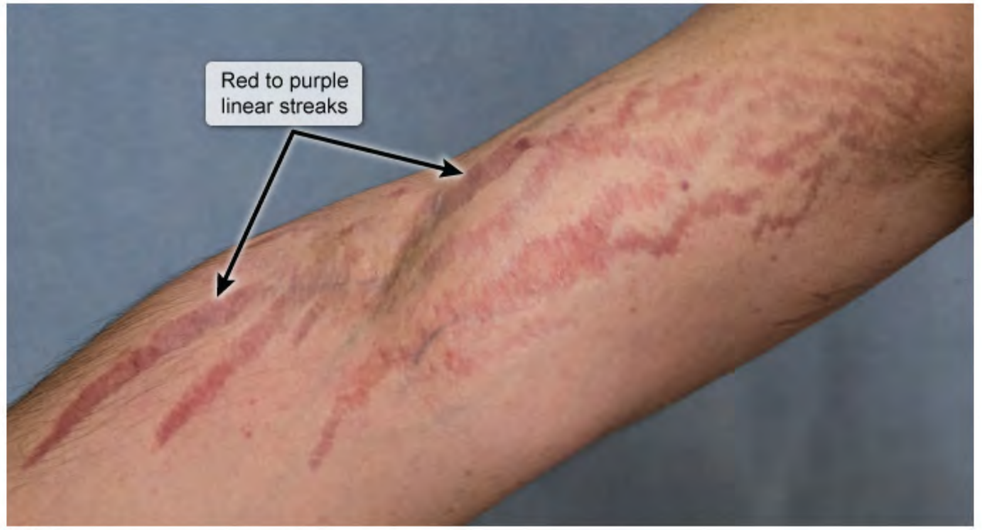
and glycogenic proteins to increase glucose availability. This, along with peripheral antagonism of insulin, contributes to the development of hyperglycemia.

https://t.me/USMLEWorldStep1

Glucocorticoids (eg, prednisone) are potent stimulators of liver **gluconeogenesis** and upregulate the synthesis of key

Exhibit Display

Glucocorticoid-induced striae



©UWorld

Zoom In Zoom Out Reset New | Existing My Notebook

and glycogenic proteins to increase glucose availability. This, along with peripheral antagonism of insulin, contributes to the development of hyperglycemia.

https://t.me/USMLEWorldStep1

A 28-year-old woman comes to the office due to unintentional weight loss, fatigue, and sweating. The patient has no neck pain. Two months before this visit, she delivered a healthy male baby without complications. The patient has no chronic medical conditions and takes no medications. Blood pressure is 140/70 mm Hg, pulse is 110/min, and respirations are 16/min. Oxygen saturation is 98% on room air. Neck examination shows mild, diffuse enlargement of the thyroid gland with no tenderness. The remainder of the physical examination is normal. Laboratory evaluation shows low serum TSH and elevated serum thyroxine (T4) and triiodothyronine (T3). Thyroid ultrasound with Doppler flow reveals a mildly enlarged gland with decreased blood flow. Which of the following is most likely responsible for this patient's disorder?

- A. Antibodies stimulating the TSH receptor
- B. Autonomous production of thyroid hormones
- C. Exogenous thyroxine intake
- D. Release of preformed thyroid hormones
- E. Viral infection of the thyroid gland

Submit

https://t.me/USMLEWorldStep1

A 28-year-old woman comes to the office due to unintentional weight loss, fatigue, and sweating. The patient has no neck pain. Two months before this visit, she delivered a healthy male baby without complications. The patient has no chronic medical conditions and takes no medications. Blood pressure is 140/70 mm Hg, pulse is 110/min, and respirations are 16/min. Oxygen saturation is 98% on room air. Neck examination shows mild, diffuse enlargement of the thyroid gland with no tenderness. The remainder of the physical examination is normal. Laboratory evaluation shows low serum TSH and elevated serum thyroxine (T4) and triiodothyronine (T3). Thyroid ultrasound with Doppler flow reveals a mildly enlarged gland with decreased blood flow. Which of the following is most likely responsible for this patient's disorder?

- ✗ A. Antibodies stimulating the TSH receptor (34%)
- B. Autonomous production of thyroid hormones (15%)
- C. Exogenous thyroxine intake (4%)
- ✓ D. Release of preformed thyroid hormones (43%)
- E. Viral infection of the thyroid gland (2%)

Incorrect
Correct answer
D

43%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

Differentiation of primary hyperthyroidism

	Increased TH synthesis	Release of preformed TH
Primary disorders	• Graves disease • Toxic nodules	• Silent (sporadic) thyroiditis • Postpartum thyroiditis • Subacute (postviral) thyroiditis

https://t.me/USMLEWorldStep1

Explanation

Differentiation of primary hyperthyroidism		
	Increased TH synthesis	**Release of preformed TH**
Primary disorders	• Graves disease • Toxic nodules	• Silent (sporadic) thyroiditis • Postpartum thyroiditis • Subacute (postviral) thyroiditis
TH (thyroxine, triiodothyronine)	↑	↑
TSH	↓	↓
Thyroglobulin	↑	↑/↑↑
Radioiodine uptake	↑	↓
Doppler ultrasound	↑ Blood flow	↓ Blood flow
Other features	• Positive TRAb/TSI (Graves) • Ophthalmopathy (Graves)	• Positive TPO (silent/postpartum) • Tender goiter (subacute) • ≤1 yr after pregnancy (postpartum)
TH = thyroid hormone; **TPO** = thyroid peroxidase antibody; **TRAb** = thyrotropin receptor antibody; **TSI** = thyroid-stimulating immunoglobulin.		

This patient has **postpartum thyroiditis** (PPT) presenting with **hyperthyroidism** (ie, elevated thyroid hormone levels, suppressed TSH) and a diffuse, **nontender goiter**. The clinical course typically has 3 phases: hyperthyroid phase (1-3 months) due to **release of preformed thyroid hormone**, hypothyroid phase (4-8 months) due to depletion of thyroid hormone stores, and recovery phase with return to euthyroid state. Not all 3 phases occur in all patients.

PPT is an **autoimmune disorder** characterized by lymphocytic thyroid inflammation. By convention, it occurs

https://t.me/USMLEWorldStep1

TH = thyroid hormone; **TPO** = thyroid peroxidase antibody; **TRAb** = thyrotropin receptor antibody; **TSI** = thyroid-stimulating immunoglobulin.

This patient has **postpartum thyroiditis** (PPT) presenting with **hyperthyroidism** (ie, elevated thyroid hormone levels, suppressed TSH) and a diffuse, **nontender goiter**. The clinical course typically has 3 phases: hyperthyroid phase (1-3 months) due to **release of preformed thyroid hormone**, hypothyroid phase (4-8 months) due to depletion of thyroid hormone stores, and recovery phase with return to euthyroid state. Not all 3 phases occur in all patients.

PPT is an **autoimmune disorder** characterized by lymphocytic thyroid inflammation. By convention, it occurs within 12 months of pregnancy. PPT is part of a group of lymphocytic/autoimmune thyroid disorders that also includes silent thyroiditis (sporadic, not related to pregnancy) and chronic lymphocytic (Hashimoto) thyroiditis (usually diagnosed in hypothyroid phase, which may be permanent). These disorders share a characteristic pattern in diagnostic testing:

- **Positive thyroid peroxidase antibody**, a nonspecific marker for autoimmune thyroid disease
- **Elevated serum thyroglobulin** due to destruction of follicles and release of colloid in the hyperthyroid phase
- **Low radioiodine uptake** due to decreased organification of iodine and synthesis of new thyroid hormone
- Diffuse swelling and decreased thyroid blood flow on ultrasound

(Choices A and B) Graves disease is caused by autoantibodies that bind and stimulate the TSH receptor (ie, thyrotropin receptor antibodies/thyroid-stimulating immunoglobulins) on thyroid follicular cells. Toxic adenoma and toxic nodular goiter are characterized by autonomous thyroid hormone synthesis. Because of the increased metabolic activity in these conditions, Doppler ultrasound reveals increased, not decreased, blood flow. Radioiodine uptake is also increased.

(Choice C) Thyrotoxicosis due to exogenous thyroid hormone use (eg, erroneous levothyroxine dosing, surreptitious use of thyroid hormone supplements) would show suppression of TSH and decreased blood flow in the thyroid, but goiter would not be present (thyroid atrophy is more likely).

(Choice E) Subacute (ie, postviral/granulomatous/de Quervain) thyroiditis is thought to be due to a viral infection in the gland or a secondary inflammatory response to viral antigens. Patients may experience a transient

https://t.me/USMLEWorldStep1

includes silent thyroiditis (sporadic, not related to pregnancy) and chronic lymphocytic (Hashimoto) thyroiditis (usually diagnosed in hypothyroid phase, which may be permanent). These disorders share a characteristic pattern in diagnostic testing:

- **Positive thyroid peroxidase antibody**, a nonspecific marker for autoimmune thyroid disease
- **Elevated serum thyroglobulin** due to destruction of follicles and release of colloid in the hyperthyroid phase
- **Low radioiodine uptake** due to decreased organification of iodine and synthesis of new thyroid hormone
- Diffuse swelling and decreased thyroid blood flow on ultrasound

(Choices A and B) Graves disease is caused by autoantibodies that bind and stimulate the TSH receptor (ie, thyrotropin receptor antibodies/thyroid-stimulating immunoglobulins) on thyroid follicular cells. Toxic adenoma and toxic nodular goiter are characterized by autonomous thyroid hormone synthesis. Because of the increased metabolic activity in these conditions, Doppler ultrasound reveals increased, not decreased, blood flow. Radioiodine uptake is also increased.

(Choice C) Thyrotoxicosis due to exogenous thyroid hormone use (eg, erroneous levothyroxine dosing, surreptitious use of thyroid hormone supplements) would show suppression of TSH and decreased blood flow in the thyroid, but goiter would not be present (thyroid atrophy is more likely).

(Choice E) Subacute (ie, postviral/granulomatous/de Quervain) thyroiditis is thought to be due to a viral infection in the gland or a secondary inflammatory response to viral antigens. Patients may experience a transient hyperthyroid phase, but the thyroid gland is characteristically painful and tender to palpation.

Educational objective:
Postpartum thyroiditis occurs within 12 months of pregnancy and is characterized by autoimmune destruction of thyroid follicles. It typically has a hyperthyroid phase due to release of preformed thyroid hormone, followed by a hypothyroid phase due to depletion of thyroid hormone stores and eventual return to a euthyroid state. Thyroid metabolic activity during the hyperthyroid phase is suppressed, and glandular blood flow and radioiodine uptake are low.

Subject	System	Topic
Pathophysiology	Endocrine, Diabetes & Metabolism	Thyroiditis

https://t.me/USMLEWorldStep1

Other features	• Positive TRAb/TSI (Graves)	• Positive TPO (silent/postpartum) • Tender goiter (subacute)

Exhibit Display

Differential diagnosis of thyroiditis

Painful thyroiditis Pain & tenderness Systemic symptoms	**Painless thyroiditis** Autoimmune/+TPO antibody Destruction of follicles Release of preformed hormone & thyroglobulin	**Graves** +TSI/TRAb ↑ Thyroid hormone synthesis	**Fibrotic** Replacement of follicles with fibrotic tissue
Subacute (granulomatous, DeQuervain) • Tender goiter • Transient hyperthyroid phase • Postviral syndrome **Acute** (suppurative) • Fever • Asymmetry • Fluctuance	**Chronic lymphocytic** (Hashimoto) • Common • Usually hypothyroid at diagnosis **Postpartum** • ≤12 months after parturition • Transient hyperthyroid phase	**Graves disease** • Overt hyperthyroidism • ↑ RAIU • Ophthalmopathy	**Riedel thyroiditis** • Hard/fixed goiter • Compression of esophagus & trachea

TPO = thyroid peroxidase; **TSI** = thyroid-stimulating immunoglobulin;
TRAb = thyrotropin receptor antibody; **RAIU** = radioiodine uptake.

©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

This p
levels,
phase
deplet
all pati

PPT is
within
includ
(usual
patter

- **P**
- **E**
- **L**
- D

(Choi
thyrotr
toxic n
metab
Radioi

(Choice C) Thyrotoxicosis due to exogenous thyroid hormone use (eg, erroneous levothyroxine dosing,

https://t.me/USMLEWorldStep1

A 42-year-old man with a long history of type 1 diabetes mellitus comes to the office due to frequent involuntary loss of urine. For the past several months, he has been having difficulty starting and maintaining a urinary stream. In the last 3 weeks, he has had 2 episodes of nocturnal enuresis and multiple daytime episodes of uncontrolled voiding without any sensation of a full bladder. His other medical problems include chronic kidney disease and gastroparesis. He does not use tobacco or alcohol. Which of the following additional findings would most likely be present in this patient?

- A. Enlarged prostate on rectal examination
- B. Increased postvoid residual volume
- C. Loss of sensation in perineal area
- D. Lower extremity hyperreflexia
- E. Mini-mental state examination score of 22

Submit

https://t.me/USMLEWorldStep1

A 42-year-old man with a long history of type 1 diabetes mellitus comes to the office due to frequent involuntary loss of urine. For the past several months, he has been having difficulty starting and maintaining a urinary stream. In the last 3 weeks, he has had 2 episodes of nocturnal enuresis and multiple daytime episodes of uncontrolled voiding without any sensation of a full bladder. His other medical problems include chronic kidney disease and gastroparesis. He does not use tobacco or alcohol. Which of the following additional findings would most likely be present in this patient?

- A. Enlarged prostate on rectal examination (12%)
- ✓ B. Increased postvoid residual volume (41%)
- C. Loss of sensation in perineal area (36%)
- D. Lower extremity hyperreflexia (8%)
- E. Mini-mental state examination score of 22 (0%)

Correct | 41% Answered correctly | 03 secs Time Spent | 2023 Version

Explanation

This patient's findings suggest **overflow incontinence**, which is mainly due to **impaired detrusor contractility** or **bladder outlet obstruction** (eg, tumor obstructing the urethra). Patients usually develop involuntary and continuous urinary leakage when the bladder is full and often have incomplete emptying. This patient's overflow incontinence is most likely due to diabetic autonomic neuropathy affecting detrusor muscle innervation, which is common in type 1 diabetics.

Patients initially have infrequent urination due to loss of autonomic afferent innervation and inability to sense a full bladder. Involvement of efferent fibers to the bladder subsequently causes incomplete emptying. Patients can develop recurrent urinary tract infections (UTIs) and overflow incontinence with poor urinary stream and dribbling.

https://t.me/USMLEWorldStep1

This patient's findings suggest **overflow incontinence**, which is mainly due to **impaired detrusor contractility** or **bladder outlet obstruction** (eg, tumor obstructing the urethra). Patients usually develop involuntary and continuous urinary leakage when the bladder is full and often have incomplete emptying. This patient's overflow incontinence is most likely due to diabetic autonomic neuropathy affecting detrusor muscle innervation, which is common in type 1 diabetics.

Patients initially have infrequent urination due to loss of autonomic afferent innervation and inability to sense a full bladder. Involvement of efferent fibers to the bladder subsequently causes incomplete emptying. Patients can develop recurrent urinary tract infections (UTIs) and overflow incontinence with poor urinary stream and dribbling. Pelvic floor relaxation at night combined with a full bladder can lead to nocturnal enuresis. Postvoid residual (PVR) testing with ultrasound or catheterization can confirm inadequate bladder emptying.

(Choice A) Enlarged prostate on rectal examination may indicate either benign prostatic hyperplasia or prostate cancer, which causes urge incontinence (bladder irritation from the enlarged prostate) or overflow incontinence (urethral obstruction). However, these conditions are commonly seen in older individuals (age >50-60).

(Choice C) Loss of sensation in the perineal area (saddle anesthesia) can indicate cauda equina syndrome, which is commonly due to epidural cord compression from a malignancy. Patients usually develop urinary retention late in the course of the disease, usually associated with fecal incontinence.

(Choices D and E) Cognitive impairment (mini-mental status examination score ≤22) is often seen in normal pressure hydrocephalus, and lower extremity hyperreflexia would suggest spinal cord disease. Both of these conditions can cause loss of central nervous system inhibition of detrusor contraction, leading to urge incontinence. Urge incontinence is characterized by a sudden desire to urinate. However, absence of other symptoms (eg, gait disturbance) in this patient makes these conditions less likely.

Educational objective:
Diabetic autonomic neuropathy is common in type 1 diabetics and can cause overflow incontinence due to inability to sense a full bladder and incomplete emptying. Postvoid residual (PVR) testing with ultrasound or catheterization can confirm inadequate bladder emptying.

References

- Diagnosis of urinary incontinence

https://t.me/USMLEWorldStep1

A 27-year-old man comes to the office for an infertility evaluation. He and his wife have been trying to conceive for the last 16 months. A previous evaluation of his wife showed no abnormalities. The patient has no prior medical conditions and takes no medications. Height is 188 cm (6' 2") and weight is 75 kg (165.3 lb). BMI is 21 kg/m^2. On physical examination, heart and lung sounds are normal. There is bilateral gynecomastia, and genital examination shows small, firm testes. The lower extremities appear abnormally long. Further evaluation will most likely show which of the following sets of findings in this patient?

	Serum LH	Serum FSH	Serum testosterone	Sperm count
A.	Decreased	Decreased	Decreased	Decreased
B.	Normal	Normal	Normal	Absent
C.	Decreased	Normal	Increased	Decreased
D.	Increased	Increased	Decreased	Absent
E.	Normal	Increased	Normal	Decreased

Submit

https://t.me/USMLEWorldStep1

A 27-year-old man comes to the office for an infertility evaluation. He and his wife have been trying to conceive for the last 16 months. A previous evaluation of his wife showed no abnormalities. The patient has no prior medical conditions and takes no medications. Height is 188 cm (6' 2") and weight is 75 kg (165.3 lb). BMI is 21 kg/m². On physical examination, heart and lung sounds are normal. There is bilateral gynecomastia, and genital examination shows small, firm testes. The lower extremities appear abnormally long. Further evaluation will most likely show which of the following sets of findings in this patient?

		Serum LH	Serum FSH	Serum testosterone	Sperm count	
✗	A.	Decreased	Decreased	Decreased	Decreased	(21%)
	B.	Normal	Normal	Normal	Absent	(1%)
	C.	Decreased	Normal	Increased	Decreased	(2%)
✓	D.	Increased	Increased	Decreased	Absent	(68%)
	E.	Normal	Increased	Normal	Decreased	(5%)

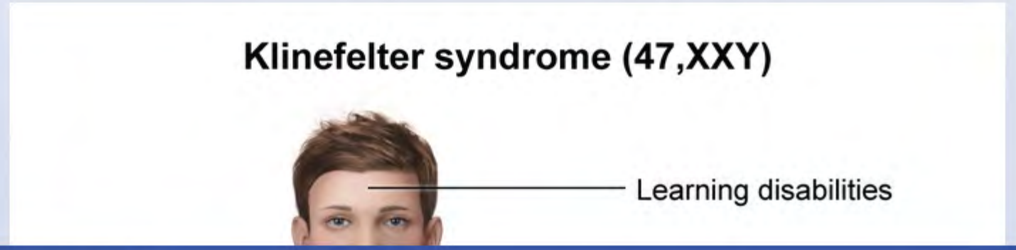
Incorrect
Correct answer
D

68%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

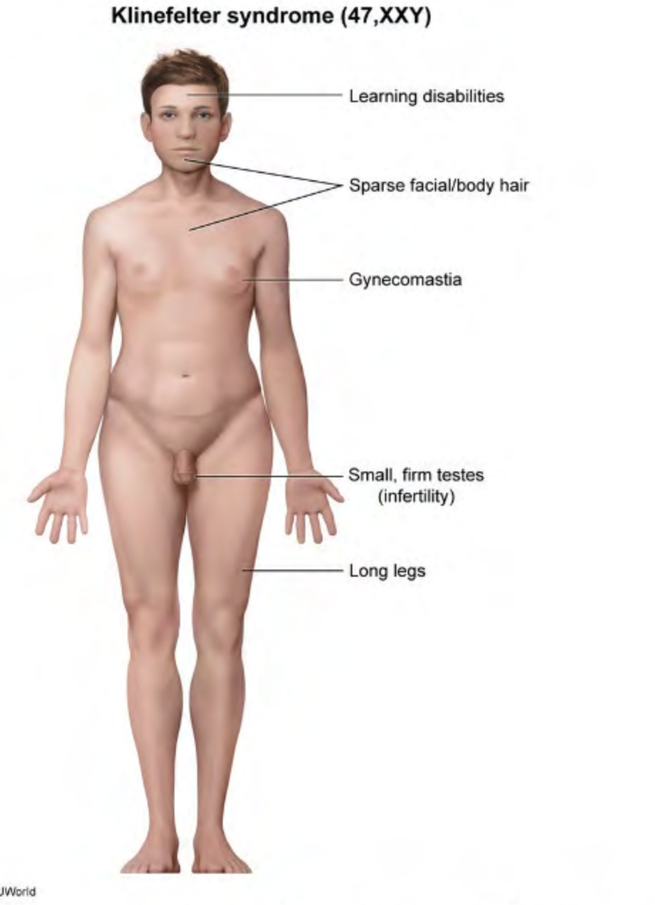


https://t.me/USMLEWorldStep1

Incorrect
Corre
D

Expl

Exhibit Display



Zoom In Zoom Out Reset New | Existing My Notebook

https://t.me/USMLEWorldStep1

This patient has infertility, **gynecomastia**, and **long lower extremities**, findings which together are highly suggestive of **Klinefelter syndrome**. Klinefelter syndrome is a chromosomal disorder (47,XXY) that can lead to **azoospermia** and infertility, although individuals with mosaic variants may have variable degrees of spermatogenesis. Common nonreproductive manifestations include intellectual and language impairment.

Klinefelter syndrome is the most common cause of male hypogonadism and is characterized by progressive destruction and hyalinization of the seminiferous tubules, leading to small, firm testes. Serum **inhibin levels are decreased** as a result of the Sertoli cell damage; Leydig cells are usually dysfunctional as well, resulting in **reduced testosterone** levels. The loss of feedback inhibition leads to **increased FSH and LH secretion**. Gynecomastia is caused by an increased ratio of estrogens to androgens (high gonadotropin levels increase aromatase activity, which increases conversion of testosterone to estradiol).

(Choice A) Hypogonadotropic (central) hypogonadism is caused by injury or dysfunction of the hypothalamus (eg, Kallmann syndrome) or pituitary gland (eg, adenomas). LH, FSH, and testosterone levels are all low, and spermatogenesis is impaired. Unlike in this patient, testes in central hypogonadism are atrophic and soft (not hyalinized and firm), and gynecomastia is uncommon because the decrease in gonadotropins reduces aromatase activity.

(Choice B) Azoospermia associated with a normal hormonal profile suggests an obstruction along the path from the testes to the seminal fluid (eg, congenital absence of the vas deferens in cystic fibrosis). In these patients, the testes and breasts are grossly normal.

(Choice C) Decreased LH, normal FSH, and elevated testosterone in the setting of a low sperm count suggest exogenous testosterone use. High androgen levels suppress LH secretion, decreasing endogenous testosterone production. Despite the high circulating levels of exogenous androgen, these patients have a low sperm count because local androgen concentrations in the seminiferous tubule are suboptimal for spermatogenesis. Over time, this leads to atrophy of the seminiferous tubules and soft, small testes.

(Choice E) Normal LH and testosterone, elevated FSH, and a low sperm count can be seen in patients with cryptorchidism. In this condition, the seminiferous tubules are damaged (resulting in elevated FSH levels), and the interstitial Leydig cells are preserved (maintaining normal LH and testosterone levels).

Educational objective:

https://t.me/USMLEWorldStep1

Klinefelter syndrome is the most common cause of male hypogonadism and is characterized by progressive destruction and hyalinization of the seminiferous tubules, leading to small, firm testes. Serum **inhibin levels are decreased** as a result of the Sertoli cell damage; Leydig cells are usually dysfunctional as well, resulting in **reduced testosterone** levels. The loss of feedback inhibition leads to **increased FSH and LH secretion**. Gynecomastia is caused by an increased ratio of estrogens to androgens (high gonadotropin levels increase aromatase activity, which increases conversion of testosterone to estradiol).

(Choice A) Hypogonadotropic (central) hypogonadism is caused by injury or dysfunction of the hypothalamus (eg, Kallmann syndrome) or pituitary gland (eg, adenomas). LH, FSH, and testosterone levels are all low, and spermatogenesis is impaired. Unlike in this patient, testes in central hypogonadism are atrophic and soft (not hyalinized and firm), and gynecomastia is uncommon because the decrease in gonadotropins reduces aromatase activity.

(Choice B) Azoospermia associated with a normal hormonal profile suggests an obstruction along the path from the testes to the seminal fluid (eg, congenital absence of the vas deferens in cystic fibrosis). In these patients, the testes and breasts are grossly normal.

(Choice C) Decreased LH, normal FSH, and elevated testosterone in the setting of a low sperm count suggest exogenous testosterone use. High androgen levels suppress LH secretion, decreasing endogenous testosterone production. Despite the high circulating levels of exogenous androgen, these patients have a low sperm count because local androgen concentrations in the seminiferous tubule are suboptimal for spermatogenesis. Over time, this leads to atrophy of the seminiferous tubules and soft, small testes.

(Choice E) Normal LH and testosterone, elevated FSH, and a low sperm count can be seen in patients with cryptorchidism. In this condition, the seminiferous tubules are damaged (resulting in elevated FSH levels), and the interstitial Leydig cells are preserved (maintaining normal LH and testosterone levels).

Educational objective:
Klinefelter syndrome (47,XXY) causes infertility characterized by primary hypogonadism (elevated FSH and LH, low testosterone) and azoospermia. Other findings include long lower extremities; small, firm testes; and gynecomastia.

https://t.me/USMLEWorldStep1

This patient has infertility, **gynecomastia**, and **long lower extremities**, findings which together are highly suggestive of **Klinefelter syndrome**. Klinefelter syndrome is a chromosomal disorder (47,XXY) that can lead to **azoos**

sperm

Klinefe

destru

decre

reduc

Gynec

aroma

(Choi

Kallma

sperm

hyalini

activity

(Choi

the tes

testes

(Choi

exoge

produc

becau

this le

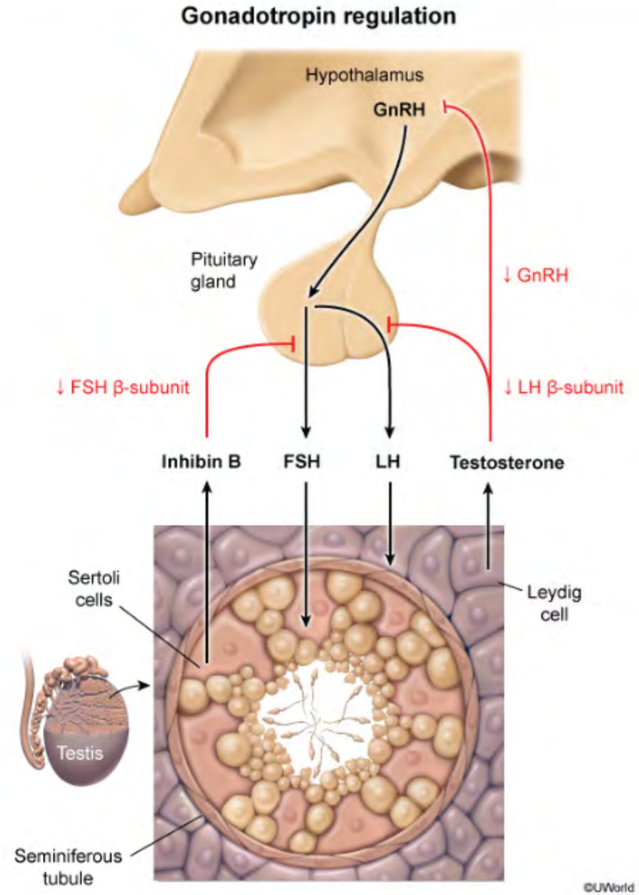
(Choi

crypto

interst

Educational objective:

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

https://t.me/USMLEWorldStep1

A 25-year-old man comes to the office for evaluation of facial acne. He has no significant past medical history and does not use tobacco or alcohol. The patient works as a personal trainer. His family history is significant for diabetes mellitus in his mother and leukemia in his father. His blood pressure is 134/82 mm Hg and pulse is 58/min. On physical examination, there is mild facial acne. The patient's lungs are clear to auscultation. The liver span is 8 cm, and the spleen is not palpable. His testes are soft, and testicular volume is decreased. Laboratory results are as follows:

Hematocrit	60%
White blood cells	7,500/mm^3
Platelets	225,000/mm^3
Erythrocyte sedimentation rate	15 mm/hr
Serum creatinine	1.2 mg/dL
Blood urea nitrogen	18 mg/dL

Which of the following is the most likely explanation for this patient's abnormal laboratory findings?

- A. High oxygen affinity hemoglobin
- B. Intensive exercise schedule
- C. Myeloproliferative disorder
- D. Renal artery stenosis
- E. Steroid drug abuse
- F. Volume depletion due to excessive sweating

Submit

https://t.me/USMLEWorldStep1

A 25-year-old man comes to the office for evaluation of facial acne. He has no significant past medical history and does not use tobacco or alcohol. The patient works as a personal trainer. His family history is significant for diabetes mellitus in his mother and leukemia in his father. His blood pressure is 134/82 mm Hg and pulse is 58/min. On physical examination, there is mild facial acne. The patient's lungs are clear to auscultation. The liver span is 8 cm, and the spleen is not palpable. His testes are soft, and testicular volume is decreased. Laboratory results are as follows:

Hematocrit	60%
White blood cells	7,500/mm^3
Platelets	225,000/mm^3
Erythrocyte sedimentation rate	15 mm/hr
Serum creatinine	1.2 mg/dL
Blood urea nitrogen	18 mg/dL

Which of the following is the most likely explanation for this patient's abnormal laboratory findings?

- ✗ A. High oxygen affinity hemoglobin (1%)
- B. Intensive exercise schedule (4%)
- C. Myeloproliferative disorder (3%)
- D. Renal artery stenosis (1%)
- ✓ E. Steroid drug abuse (86%)
- F. Volume depletion due to excessive sweating (3%)

Incorrect
Correct answer
E

86%
Answered correctly

03 secs
Time Spent

2023
Version

https://t.me/USMLEWorldStep1

Incorrect
Correct answer
E

86%
03 secs
2023

Exhibit Display

Effects of androgen abuse	
Cardiovascular	• ↑ **Hematocrit** • ↑ LDL, ↓ HDL cholesterol
Dermatologic	• **Acne** • Hirsutism, male-pattern hair loss (♀)
Genitourinary	• Clitoromegaly, oligomenorrhea (♀) • **Testicular atrophy**, ↓ spermatogenesis (♂)
Psychiatric	• Depression, hypomania (♀) • Aggressiveness, mood disorders (♂)
Breast	• Atrophy (♀) • **Gynecomastia** (♂)
Other	• **Deepening of voice** (♀) • Premature epiphyseal closure (adolescents)

©UWorld

Zoom In Zoom Out Reset New | Existing My Notebook

Expl

This p
Abuse
comm

Chron
blood cell production, which accounts for the higher hematocrit in normal males compared to normal females. This effect is exaggerated in exogenous androgen abuse, which **increases hematocrit** in a dose-dependent manner.

https://t.me/USMLEWorldStep1

This patient has acne, testicular atrophy, and erythrocytosis, findings concerning for **androgenic steroid abuse**. Abuse of androgens, androgen precursors, and agents that increase endogenous androgen production is most common in young adults who engage in competitive athletic activities or for cosmetic purposes.

Chronic androgen use may increase muscle mass but has multiple associated risks. Testosterone stimulates red blood cell production, which accounts for the higher hematocrit in normal males compared to normal females. This effect is exaggerated in exogenous androgen abuse, which **increases hematocrit** in a dose-dependent manner. Androgens decrease gonadotropin secretion, which results in **testicular atrophy** and decreased sperm production. Other common findings include **virilization** in women (eg, clitoromegaly, hirsutism) and **acne**.

(Choices A and D) Mutations that cause a high oxygen affinity of hemoglobin reduce the ability of hemoglobin to release oxygen in tissues. Low tissue oxygen levels in the kidneys stimulate erythropoietin release. Renal artery stenosis decreases oxygen delivery to the kidney and also stimulates erythropoietin release. These conditions may produce a compensatory erythrocytosis but would not produce the other clinical signs (eg, acne, testicular atrophy) seen in this patient.

(Choice B) Intensive exercise could result in elevated myoglobin secondary to rhabdomyolysis, but the hematocrit level should not be changed by exercise.

(Choice C) Myeloproliferative disorders, such as polycythemia vera (PV), can lead to erythrocytosis. Patients with PV typically have leukocytosis and thrombocytosis as well. This patient's additional physical findings make steroid abuse more likely.

(Choice F) Heavy sweating may cause a transient increase in hematocrit due to loss of plasma volume but would likely cause other signs of dehydration (eg, tachycardia). This patient's creatinine at the upper limit of normal is typical for patients with increased total muscle mass; hypovolemia also will usually cause a more pronounced rise in blood urea nitrogen.

Educational objective:
Androgenic steroid abuse may lead to erythrocytosis, testicular atrophy, acne, and virilization in women (eg, clitoromegaly, hirsutism).

References

https://t.me/USMLEWorldStep1

A 17-year-old girl is brought to the clinic due to irregular menses. Menarche was at age 12 and her cycles since then have been irregular, often with multiple months between menstrual periods. The patient also has had an increase in hair growth along her chest and face. Temperature is 37.3 C (99.1 F), blood pressure is 110/70 mm Hg, and pulse is 80/min. There are dark, terminal hairs above the patient's upper lip and nodulocystic acne across her forehead. Cardiopulmonary examination is normal. Sexual maturity rating (Tanner stage) is 5. Ultrasound examination of the pelvis reveals a normal uterus and ovaries. Electrolytes are normal; other laboratory results are as follows:

Testosterone, serum	400 ng/dL	(normal: 25-75 ng/dL)
17-hydroxyprogesterone	350 ng/dL	(normal: <200 ng/dL)

Which of the following enzyme reaction steps is most likely to be disrupted in this patient?

- A. 11-deoxycorticosterone conversion to corticosterone
- B. 11-deoxycortisol conversion to cortisol
- C. Pregnenolone conversion to 17-hydroxypregnenolone
- D. Progesterone conversion to 11-deoxycorticosterone
- E. Testosterone conversion to estradiol

Submit

https://t.me/USMLEWorldStep1

A 17-year-old girl is brought to the clinic due to irregular menses. Menarche was at age 12 and her cycles since then have been irregular, often with multiple months between menstrual periods. The patient also has had an increase in hair growth along her chest and face. Temperature is 37.3 C (99.1 F), blood pressure is 110/70 mm Hg, and pulse is 80/min. There are dark, terminal hairs above the patient's upper lip and nodulocystic acne across her forehead. Cardiopulmonary examination is normal. Sexual maturity rating (Tanner stage) is 5. Ultrasound examination of the pelvis reveals a normal uterus and ovaries. Electrolytes are normal; other laboratory results are as follows:

Testosterone, serum	400 ng/dL	(normal: 25-75 ng/dL)
17-hydroxyprogesterone	350 ng/dL	(normal: <200 ng/dL)

Which of the following enzyme reaction steps is most likely to be disrupted in this patient?

- ✗ A. 11-deoxycorticosterone conversion to corticosterone (12%)
- B. 11-deoxycortisol conversion to cortisol (11%)
- C. Pregnenolone conversion to 17-hydroxypregnenolone (9%)
- ✓ D. Progesterone conversion to 11-deoxycorticosterone (38%)
- E. Testosterone conversion to estradiol (27%)

Incorrect
Correct answer
D

38%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

21-Hydroxylase deficiency clinical syndromes			
	Classic,	Classic,	Nonclassic,

https://t.me/USMLEWorldStep1

21-Hydroxylase deficiency clinical syndromes			
	Classic, salt wasting	**Classic, non–salt wasting***	**Nonclassic, late onset**
Enzyme deficiency	Severe	Moderate	Mild
Clinical features	• Birth (girls): ambiguous genitalia • Age 1-2 weeks: vomiting, hypotension, hyperkalemia	• Birth (girls): ambiguous genitalia • Age 2-4: virilization (eg, body odor, pubic/axillary hair) & rapid growth	• School-aged: premature pubarche & rapid growth • Adolescence (girls): hirsutism, acne, oligomenorrhea
Laboratory features	• Increased 17-hydroxyprogesterone • Increased testosterone		
*Also called simple virilizing form.			

This patient's laboratory findings are consistent with **21-hydroxylase deficiency**, the most common cause of congenital adrenal hyperplasia (CAH). The 21-hydroxylase enzyme is responsible for conversion of **progesterone to 11-deoxycorticosterone** and 17-hydroxyprogesterone (17-OHP) to 11-deoxycortisol. Enzyme deficiency causes the **buildup of 17-OHP**, which is then shunted toward androgen production.

Deficiency of 21-hydroxylase can result in varying clinical phenotypes depending on the amount of residual enzyme available. This patient's presentation in **adolescence** with **menstrual irregularities** and signs of **androgen excess** (ie, hirsutism, nodulocystic acne) is consistent with the mildest form, **nonclassic** (late-onset) CAH. Other common findings of nonclassic CAH include premature pubarche (ie, early appearance of pubic/axillary hair) and accelerated growth and bone age in school-aged children. Because 21-hydroxylase is not completely absent in nonclassic CAH, sufficient mineralocorticoids are produced to avoid the salt wasting (ie, hypotension, hyperkalemia) seen in neonates with severe classic CAH.

Laboratory studies in all forms of 21-hydroxylase deficiency reveal **elevated 17-OHP and testosterone** levels.

https://t.me/USMLEWorldStep1

This patient's laboratory findings are consistent with **21-hydroxylase deficiency**, the most common cause of congenital adrenal hyperplasia (CAH). The 21-hydroxylase enzyme is responsible for conversion of **progesterone to 11-deoxycorticosterone** and 17-hydroxyprogesterone (17-OHP) to 11-deoxycortisol. Enzyme deficiency causes the **buildup of 17-OHP**, which is then shunted toward androgen production.

Deficiency of 21-hydroxylase can result in varying clinical phenotypes depending on the amount of residual enzyme available. This patient's presentation in **adolescence** with **menstrual irregularities** and signs of **androgen excess** (ie, hirsutism, nodulocystic acne) is consistent with the mildest form, **nonclassic** (late-onset) CAH. Other common findings of nonclassic CAH include premature pubarche (ie, early appearance of pubic/axillary hair) and accelerated growth and bone age in school-aged children. Because 21-hydroxylase is not completely absent in nonclassic CAH, sufficient mineralocorticoids are produced to avoid the salt wasting (ie, hypotension, hyperkalemia) seen in neonates with severe classic CAH.

Laboratory studies in all forms of 21-hydroxylase deficiency reveal **elevated 17-OHP and testosterone** levels.

(Choices A and B) Patients with 11 beta-hydroxylase deficiency have impaired conversion of 11-deoxycorticosterone to corticosterone and 11-deoxycortisol to cortisol. In addition to hyperandrogenism, patients have hypertension and hypokalemia (not seen here) due to increased 11-deoxycorticosterone (a weak mineralocorticoid).

(Choice C) Conversion of pregnenolone to 17-hydroxypregnenolone is impaired with 17 alpha-hydroxylase deficiency. Patients have hypertension and hypokalemia due to increased mineralocorticoid synthesis and amenorrhea and absent secondary sexual characteristics due to absent sex hormone production. In addition, 17-OHP and testosterone are decreased with this disorder.

(Choice E) Aromatase converts testosterone to estradiol. Due to lack of estrogens, aromatase deficiency results in primary amenorrhea, absent breast development, and virilized genitalia (eg, clitoromegaly) in girls.

Educational objective:
Nonclassic congenital adrenal hyperplasia is due to mild deficiency of 21-hydroxylase, an enzyme that converts progesterone to 11-deoxycorticosterone and 17-hydroxyprogesterone to 11-deoxycortisol. In adolescent girls, it presents with signs of hyperandrogenism (eg, hirsutism, acne, menstrual irregularities) as well as increased 17-hydroxyprogesterone and testosterone levels.

https://t.me/USMLEWorldStep1

causes the **buildup of 17-OHP**, which is then shunted toward androgen production.

Deficiency of 21-hydroxylase can result in varying clinical phenotypes depending on the amount of residual enzyme available. This patient's presentation in **adolescence** with **menstrual irregularities** and signs of **androgen excess** (ie, hirsutism, nodulocystic acne) is consistent with the mildest form, **nonclassic** (late-onset) CAH. Other common findings of nonclassic CAH include premature pubarche (ie, early appearance of pubic/axillary hair) and accelerated growth and bone age in school-aged children. Because 21-hydroxylase is not completely absent in nonclassic CAH, sufficient mineralocorticoids are produced to avoid the salt wasting (ie, hypotension, hyperkalemia) seen in neonates with severe classic CAH.

Laboratory studies in all forms of 21-hydroxylase deficiency reveal **elevated 17-OHP and testosterone** levels.

(Choices A and B) Patients with 11 beta-hydroxylase deficiency have impaired conversion of 11-deoxycorticosterone to corticosterone and 11-deoxycortisol to cortisol. In addition to hyperandrogenism, patients have hypertension and hypokalemia (not seen here) due to increased 11-deoxycorticosterone (a weak mineralocorticoid).

(Choice C) Conversion of pregnenolone to 17-hydroxypregnenolone is impaired with 17 alpha-hydroxylase deficiency. Patients have hypertension and hypokalemia due to increased mineralocorticoid synthesis and amenorrhea and absent secondary sexual characteristics due to absent sex hormone production. In addition, 17-OHP and testosterone are decreased with this disorder.

(Choice E) Aromatase converts testosterone to estradiol. Due to lack of estrogens, aromatase deficiency results in primary amenorrhea, absent breast development, and virilized genitalia (eg, clitoromegaly) in girls.

Educational objective:
Nonclassic congenital adrenal hyperplasia is due to mild deficiency of 21-hydroxylase, an enzyme that converts progesterone to 11-deoxycorticosterone and 17-hydroxyprogesterone to 11-deoxycortisol. In adolescent girls, it presents with signs of hyperandrogenism (eg, hirsutism, acne, menstrual irregularities) as well as increased 17-hydroxyprogesterone and testosterone levels.

Pathophysiology	Endocrine, Diabetes & Metabolism	Congenital adrenal hyperplasia
Subject	System	Topic

https://t.me/USMLEWorldStep1

deficiency

	• Birth (girls): ambiguous	• Birth (girls): ambiguous	• School aged: premature
La			
*A			

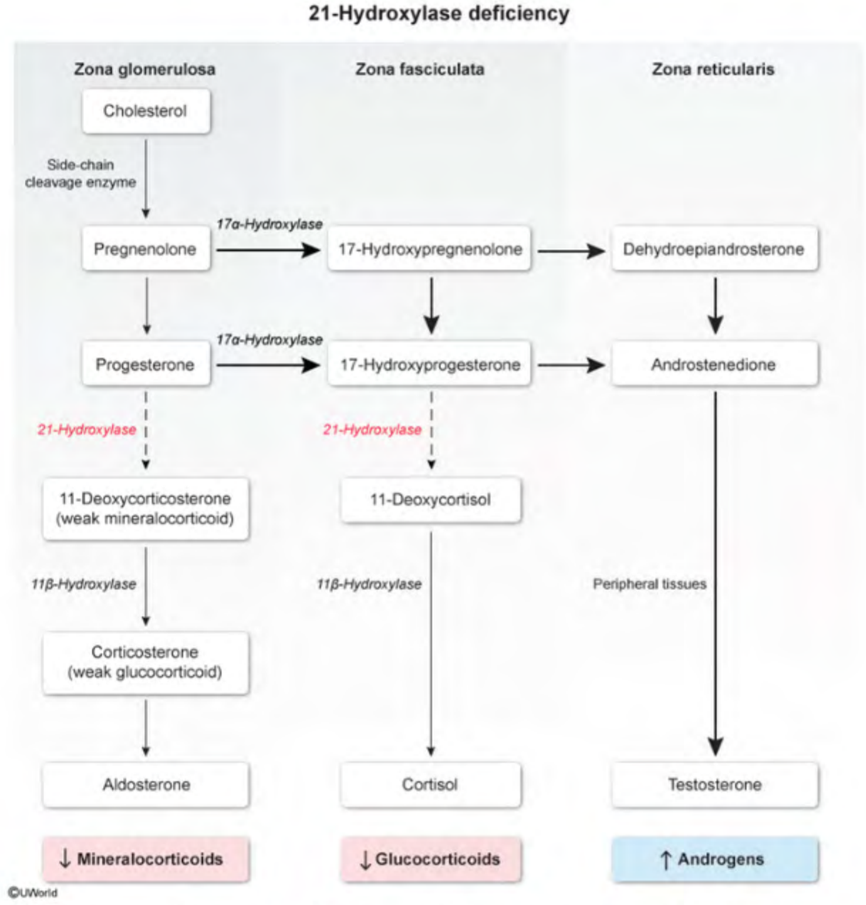
This p
conge
to 11-
cause

Deficie
enzym
andro
CAH.
pubic/
compl
hypote

Labora

(Choi
deoxy
have h
minera

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

(Choice C) Conversion of pregnenolone to 17-hydroxypregnenolone is impaired with 17 alpha-hydroxylase

https://t.me/USMLEWorldStep1

deficiency			
	• Birth (girls): ambiguous	• Birth (girls): ambiguous	• School aged: premature
La			
*A			

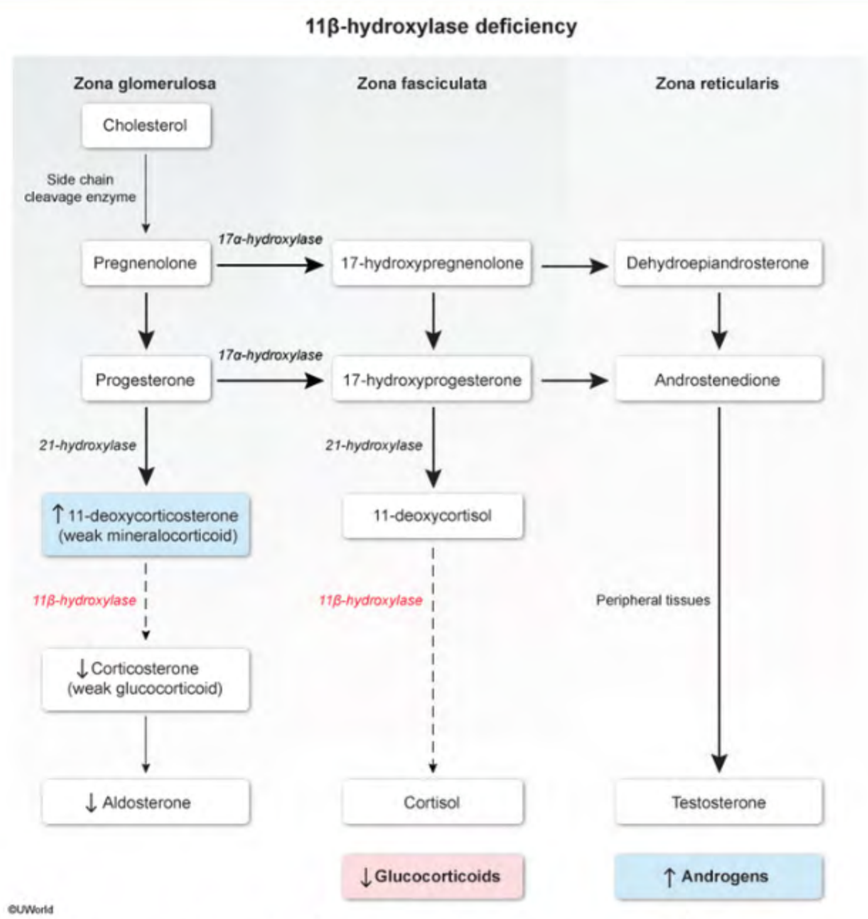
This p
conge
to 11-
cause

Deficie
enzym
andro
CAH.
pubic/
compl
hypote

Labora

(Choi
deoxy
have h
minera

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

(Choice C) Conversion of pregnenolone to 17-hydroxypregnenolone is impaired with 17 alpha-hydroxylase

https://t.me/USMLEWorldStep1

This patient's laboratory findings are consistent with **21-hydroxylase deficiency**, the most common cause of

conge

to 11-

causes

Deficie

enzym

andro

CAH.

pubic/

compl

hypote

Labora

(Choi

deoxy

have h

minera

(Choi

deficie

amenc

OHP a

(Choi

in prim

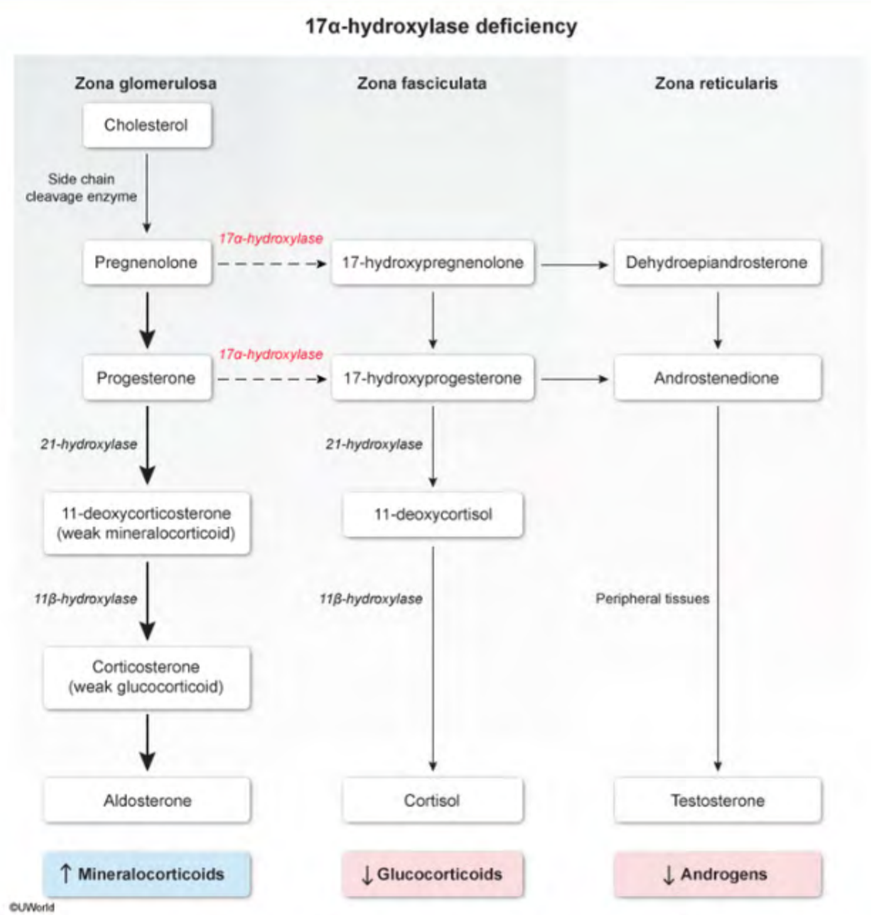
Educa

Noncla

proges

presents with signs of hyperandrogenism (eg, hirsutism, acne, menstrual irregularities) as well as increased 17-

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

causes the **buildup of 17-OHP**, which is then shunted toward androgen production.

Deficie
enzym
andro
CAH.
pubic/
compl
hypote

Labora

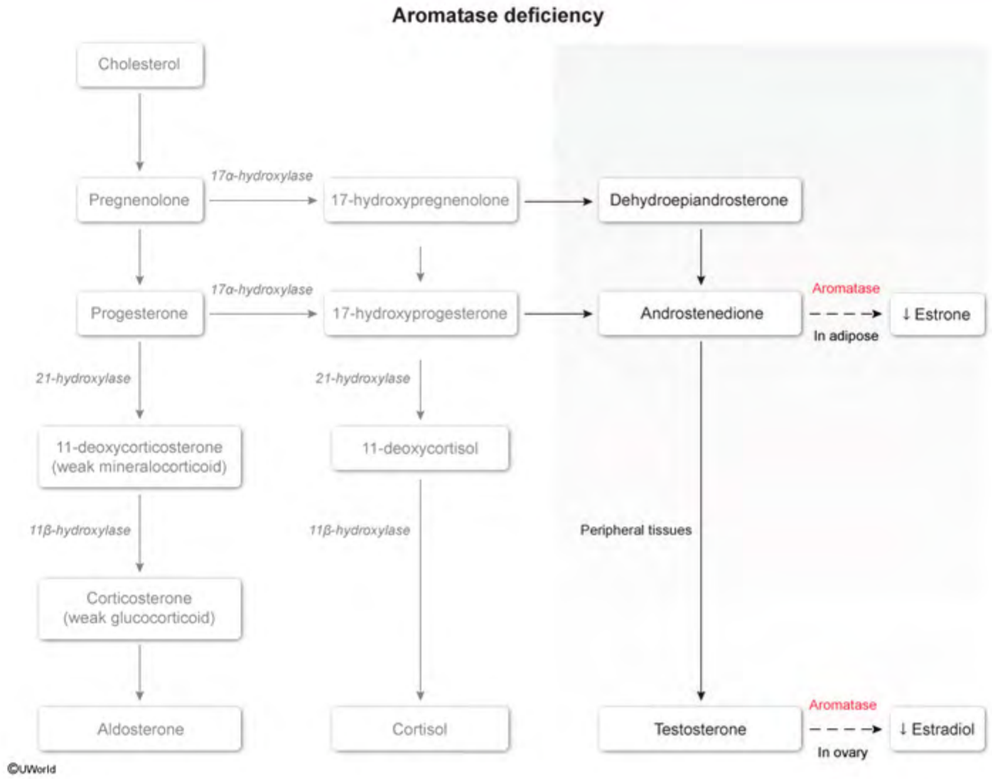
(Choi
deoxy
have h
minera

(Choi
deficie
amenc
OHP a

(Choi
in prim

Educa
Noncla
proges
preser
hydrox

Exhibit Display



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Pathophysiology
Subject

Endocrine, Diabetes & Metabolism
System

Congenital adrenal hyperplasia
Topic

https://t.me/USMLEWorldStep1